

*Gastroparesis
Clinical Research Consortium*

**Nortriptyline for Idiopathic Gastroparesis
A Multicenter, Randomized
Double-Masked, Placebo-Controlled Trial
(NORIG)**

Standard Operating Procedures

Part I: Clinical Center Operations

18 August 2011

NORIG SOP Part I: Clinical Center Operations

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1. Design overview

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1.1. Design synopsis

Title

- Nortriptyline for Idiopathic Gastroparesis: A Multicenter, Randomized, Double-Masked Placebo-Controlled Trial (NORIG)

Sponsor

- NIDDK

Type of study

- Phase III randomized clinical trial
- Multicenter, double-masked, placebo-controlled trial of 2 parallel treatment groups

Objective

- To determine whether treatment with nortriptyline or placebo results in symptomatic improvement in patients with idiopathic gastroparesis.

Treatment groups

- Group 1: Nortriptyline; 10 mg, one capsule, po qhs (by mouth at bedtime each night) x 3 weeks,
f03 visit, 25 mg, one capsule, po qhs x 3 weeks,
f06 visit, 50 mg, two capsules, po qhs x 3 weeks,
f09 visit, 75 mg, three capsules, po qhs x 6 weeks,
f15 visit: taper study drug by one capsule a week, off study drug for the last week
- Group 2: Nortriptyline-placebo, 10 mg, one capsule, po qhs x 3 weeks,
f03 visit, 25 mg, one capsule, po qhs x 3 weeks;
f06 visit, 50 mg, two capsules, po qhs x 3 weeks;
f09 visit, 75 mg, three capsules, po qhs x 6 weeks
f15 visit: taper study drug by one capsule a week, off study drug for the last week

Population

- Patients aged 21 - 65 years old at registration with moderate to severe symptoms of idiopathic gastroparesis

Study duration – per patient

- Up to 16 weeks of screening prior to randomization, including a 6 week washout period for other tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOI).
- 15 weeks of treatment starting at randomization
- Tapering off study drug by one capsule a week from 15 to 17 weeks after randomization
- One week with no study drug from 17 to 18 weeks after randomization

1.1. Design synopsis
Study duration – per calendar time

- Recruitment phase: 39 months
- Follow-up phase: 44 months

Sample size justification

- Total of 130 patients in 2 groups of equal size (65 per group)
- Primary comparison: nortriptyline vs. placebo
- Error protection: Type I = 0.05 and Type II = 0.10 (90% power)
- Minimum clinically important difference (MCID): 50% reduction in GCSI outcome (see below) during 15 weeks of treatment
 - Expected percent with improved GCSI in the placebo group: 30%
 - Expected percent with improved GCSI in the nortriptyline group: 60%
 - Source of estimates of MCID: Consensus of GpCRC clinicians
- Statistical test and sample size software
 - Chi-squared test for two proportions
 - Dupont and Plummer PS software

Number of clinical centers

- 7

Inclusion criteria

- Age 21 through 65 years old at registration
- Documentation of delayed gastric emptying on gastric emptying scintigraphy within 2 years of registration, defined as greater than 60% retention at 2 hours or greater than 10% retention at 4 hours
- Symptoms of gastroparesis for at least 6 months (does not have to be contiguous) prior to registration with Gastroparesis Cardinal Symptom Index (GCSI) score of ≥ 21
- Negative upper endoscopy or upper GI series within 2 years of registration

Exclusion criteria

- Normal gastric emptying confirmed with scintigraphy
- Diabetic gastroparesis or post-surgical gastroparesis including fundoplication
- Another active disorder which could explain symptoms in the opinion of the investigator
- History of significant cardiac arrhythmias and/or prolonged QTc
- History of seizures
- Use of narcotics more than 3 days per week
- Use of tricyclic antidepressants for refractory symptoms of gastroparesis within 6 weeks prior to randomization
- Use of strongly anticholinergic medications
- Use of calcium channel blockers
- Use of erythromycin

1.1. Design synopsis

- Clear history of failed trial of nortriptyline use for gastroparetic symptoms
- Symptoms of primary depression or suicidal ideation
- Contraindications to nortriptyline:
 - a) hypersensitivity or allergy to any tricyclic antidepressant drug
 - b) concomitant therapy with a monoamine oxidase inhibitor (MAOI)
 - c) recent myocardial infarction
 - d) glaucoma
- Pregnancy or nursing
- Any other condition, which in the opinion of the investigator would impede compliance or hinder completion of the study
- Use of a G tube, J tube, or a central catheter for nutrition
- Use of a gastric electrical stimulator
- Failure to give informed consent

Outcome measures

- **Primary:** The primary outcome measure is defined as a decrease from the baseline GCSI score (sum of the 9 individual symptom scores) of at least 50% on any two consecutive follow-up visits during the 15 week treatment period with maximum tolerated study drug dose. A sensitivity analysis will compare cumulative GCSI symptom scores averaged across all follow-up visits to rule out the possibility that an effect present in the primary analysis was due to the GCSI score decreasing 50% on two consecutive visits with smaller improvement or worsening on other follow-up visits. All patients will be followed for the full 18 weeks after randomization regardless of response or course of treatment to permit an intention-to-treat primary analysis.

The GCSI total score ranges from 0 to 45 (highest severity) and is calculated as the sum of nine individual symptom scores:

GCSI = Nausea (0-5) +
 Retching (0-5) +
 Vomiting (0-5) +
 Stomach fullness (0-5) +
 Not able to finish a normal sized meal (0-5) +
 Feeling excessively full after meals (0-5) +
 Loss of appetite (0-5) +
 Bloating (0-5) +
 Stomach visibly larger (0-5)

As noted earlier, a GCSI score of 21 or greater is a requirement for enrollment into the trial. The primary outcome measure is a binary (0, 1) variable, which equals to 1, if a GCSI score reduction of 50% or greater, relative to the baseline score, is observed on at least two

1.1. Design synopsis

consecutive follow-up visits during the 15 weeks of treatment and follow-up.

- **Secondary outcome measures** will be defined to address the following areas:
 - (1) Symptoms
 - Subscores for the GCSI such as nausea/vomiting, postprandial fullness, bloating
 - Individual symptom scores
 - Global overall relief of symptom questionnaire
 - Clinical global patient impression
 - (2) Physiology
 - Satiety test: Volume of Ensure® consumed during satiety testing
 - Electrogastrography: Percent time in EGG dysrhythmias (outside 2.5-3.75 cycles per minute)
 - Side effects to treatment requiring stopping medication

Subgroup differences in response to nortriptyline will be addressed:

- (1) Differential response to nortriptyline based on pharmacogenetic analysis of patients
- (2) Differential response to nortriptyline based on blood levels of nortriptyline

Randomization

- Centrally administered randomization stratified by clinical center and blocked by calendar time

Visit schedule

- Screening: at least 1 visit separated by at least 1 calendar day from randomization; screening period can last no more than 16 weeks after registration
- Randomization: final pre-treatment interview, dispensing of study drug
- Follow-up visits:
 - every 3 weeks after randomization throughout the 18 week study

Statistical analysis

- All analyses will be on an “intention-to-treat” basis

Safety monitoring

- NIDDK appointed DSMB will monitor the data for safety and efficacy for outcomes such as toxicity and any other outcomes or events identified as safety-related
-

1.2. Data collection schedule

Assessment/Procedure	Screening Visits			Follow-up visits Weeks from randomization					
	s1	s2	rz	3	6	9	12	15	18
Consent	X
Gastric emptying scintigraphy review	X
Upper endoscopy review	X
Baseline medical history	X
PAGI-SYM questionnaire	X	.	.	X	X	X	X	X	X
GSRS questionnaire	X	.	.	X	X	X	X	X	X
SF-36 QOL questionnaire	X	X	.	X	.
Beck Depression Inventory-II	X	.	.	X	X	X	X	X	X
State Trait Anxiety Inventory	X	X	.	X	.
Brief Pain Inventory	X	X	.	X	.
PHQ-15 questionnaire	X	X	.	X	.
Electrocardiogram (ECG)	X	X	X	.	.
Physical exam	X	.	X	.	.	X	X	X	.
Satiety test with electrogastrography (EGG)	.	X	X	.	.
Study drug dispensed	.	.	X	X	X	X	X	.	.
Review of study drug adherence	.	.	.	X	X	X	X	X	X
Follow-up medical history including review of adverse events	.	.	.	X	X	X	X	X	X
Labs
CBC, metabolic and hepatic panel	X	X	.	.
TSH	X
Plasma banking	.	X	X	X	.
DNA banking	.	X
Pregnancy test	X	.	X	.	.	X	X	X	.

Physical exam: includes measurement of weight, height, waist and hip circumferences, vital signs (temperature, heart rate, blood pressure) general physical findings

CBC: Complete blood count: white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count

Metabolic panel: sodium, potassium, chloride, carbon dioxide, glucose, calcium, magnesium, blood urea nitrogen (BUN), creatinine.

Hepatic Panel: albumin, total protein, bilirubin, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST)

TSH: Thyroid Stimulating Hormone

1.3. Whole blood draw schedule: mL of blood to be drawn at screening and follow-up visits

Procedure	Study visit (wk)								Total
	s1	s2	3	6	9	12	15	18	
Complete blood count	5	5	.	.	10
Metabolic panel	5	5	.	.	10
Hepatic panel	5	5	.	.	10
Thyroid stimulating hormone	5	5
Blood for DNA banking - including pharmacogenomic analysis	.	20	20
Blood for plasma banking - including study drug level measurement	.	10	.	.	.	10	10	.	30
Total (in mL)	20	30	0	0	0	25	10	0	85

Complete blood count: white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count

Metabolic panel: sodium, potassium, chloride, carbon dioxide, glucose, calcium, magnesium, blood urea nitrogen (BUN), creatinine

Hepatic panel: albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin

1.4. Study population composition

- 130 patients aged 21 to 65 years old at registration with:
 - Moderate to severe symptoms of idiopathic gastroparesis
 - Gastroparesis with delayed gastric emptying confirmed by scintigraphy
 - Symptoms of gastroparesis for at least 6 months
 - ~22 patients per clinical center
 - Gastroparesis must not be from diabetic or post-surgical etiologies including fundoplication
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2.1. Inclusion and exclusion criteria

Inclusion

Patients with moderate to severe symptoms of idiopathic gastroparesis will be studied. Patients should not have diabetic or post-surgical gastroparesis or dyspeptic symptoms with normal gastric emptying. In order to qualify for inclusion in the trial, patients must satisfy the following inclusion criteria:

1. Aged 21 – 65 years old at registration
2. Documentation of delayed gastric emptying on gastric emptying scintigraphy within 2 years of registration date, defined as greater than 60% retention at 2 hours or greater than 10% retention at 4 hours
3. Symptoms of gastroparesis for at least 6 months (does not have to be contiguous) prior to registration with Gastroparesis Cardinal Symptom Index (GCSI) score of ≥ 21
4. Negative upper endoscopy or upper GI series within 2 years of registration date

Exclusion

Patients who satisfy any of the following exclusion criteria will be ineligible for randomization in the trial:

1. Normal gastric emptying confirmed with scintigraphy
 2. Diabetic gastroparesis or post-surgical gastroparesis including fundoplication
 3. Another active disorder which could explain symptoms in the opinion of the investigator
 4. History of significant cardiac arrhythmias and/or prolonged QTc
 5. History of seizures
 6. Use of narcotics (including fentanyl patches) more than 3 days per week
 7. Use of tricyclic antidepressants for refractory symptoms of gastroparesis within 6 weeks prior to randomization
 8. Use of strongly anticholinergic medications
 9. Use of calcium channel blockers
 10. Use of erythromycin
 11. Clear history of failed trial of nortriptyline use for gastroparetic symptoms
 12. Symptoms of primary depression or suicidal ideation
 13. Contraindications to nortriptyline:
 - a) hypersensitivity or allergy to any tricyclic antidepressant
 - b) concomitant therapy with a monoamine oxidase inhibitor (MAOI)
 - c) recent myocardial infarction
 - d) glaucoma
 14. Pregnancy or nursing
 15. Any other condition, which in the opinion of the investigator would impede compliance or hinder the completion of the study
 16. Use of a G tube, J tube or a central catheter for nutrition
 17. Use of a gastric electrical stimulator
 18. Failure to give informed consent
-

2.2. Run-in period

Patients must not have used any tricyclic antidepressants for refractory symptoms of gastroparesis within 6 weeks prior to randomization. Patients must not have used any monoamine oxidase inhibitors (MAOIs), strongly anticholinergic drugs, calcium channel blockers, or erythromycin for the 6 weeks prior to randomization. Patients must not have used a narcotic analgesic for abdominal pain on a daily basis for the 6 weeks prior to randomization. These agents are not to be used during screening nor for the duration of the trial. Patients will be interviewed in a detailed fashion at screening, randomization, and at every follow-up study visit to document the absence of such use.

Patients will be allowed to continue on gastroparesis medications such as metacloperamide or domperidone, as well as any over-the-counter medications or dietary supplements. If the patient is currently using a selective serotonin reuptake inhibitor (SSRI), the patient must have been on a stable dose for the 3 months prior to randomization.

2.3. Calculation of Gastroparesis Cardinal Symptom Index (GCSI)

Gastroparesis Cardinal Symptom Index (GCSI) score for gastrointestinal symptoms will be calculated using the NORIG data collection form GD - Patient Assessment of Upper Gastrointestinal Disorders Symptoms Severity Index (PAGI-SYM)[®] as follows:

The GCSI score will be calculated as the sum of the three symptom sub-scale scores. GCSI score can range from 0 to 45, with higher scores reflecting greater symptom severity.

Points:

None	Very mild	Mild	Moderate	Severe	Very Severe
0	1	2	3	4	5

Nausea/vomiting subscore: (sum of these 3 items) _____

1. nausea (feeling sick to your stomach as if you were going to vomit or throw up) 0 1 2 3 4 5
2. retching (heaving as if to vomit, but nothing comes up) 0 1 2 3 4 5
3. vomiting 0 1 2 3 4 5

Postprandial fullness/early satiety subscore: (sum of these 4 items) _____

4. stomach fullness 0 1 2 3 4 5
5. not able to finish a normal-sized meal 0 1 2 3 4 5
6. feeling excessively full after meals 0 1 2 3 4 5
7. loss of appetite 0 1 2 3 4 5

Bloating subscore: (sum of these 2 items) _____

8. bloating (feeling like you need to loosen your clothes) 0 1 2 3 4 5
9. stomach or belly visibly larger 0 1 2 3 4 5

Total GCSI score: (sum of 3 subscores) _____

The total GCSI score must be ≥ 21 during screening to be eligible for randomization into the NORIG trial.

2.4. Guidelines for repeat determinations of eligibility

While certain inclusion and exclusion criteria are more objective and are unlikely to change, others are more subjective and may change over time. Thus, participants who are deemed ineligible at the time of initial screening may be re-screened at a later time as follows:

- Age <21 years – the participant may be re-screened after his or her 21st birthday
 - Symptoms of gastroparesis for less than 6 months duration – the participant may be re-screened when 6 months of gastroparesis symptoms is reached
 - Symptoms of gastroparesis with a Gastroparesis Cardinal Symptom Index (GCSI) score of < 21 – the participant may be re-screened at the discretion of the investigator
 - Use of narcotics greater than 3 days per week – participant may be re-screened when use of narcotic medications is less than or equal to 3 days per week.
 - Use of tricyclic antidepressants for refractory symptoms of gastroparesis – the participant may be re-screened after completing a 6 week washout
 - Use of a monoamine oxidase inhibitor (MAOI), calcium channel blockers, erythromycin, or strongly anticholinergic drugs – the participant may be re-screened after completing a 6 week washout
 - Use of a selective serotonin reuptake-inhibitor (SSRI) at a stable dose for less than 3 months – the participant may be re-screened after 3 months on a stable dose
 - Unwilling to participate – the participant may be re-screened at the discretion of the investigator
 - Unable to complete gastric emptying scintigraphy – the test may be repeated and the participant may be re-screened when clinically indicated
-

2.5. Co-enrollment in Gastroparesis Registry

- When a Gastroparesis Registry (GpR) participant is randomized into a GpCRC treatment trial such as NORIG, the visit schedule and requirements of the treatment trial take precedence over the requirements for the Registry. Registry requirements are suspended for the duration of the participant's time in the treatment trial. The GpR Closeout Form (CO) should be completed after the patient is fully enrolled or randomized into the treatment trial to suspend the Registry visits.

Patient enrolled in GpR who now wants to screen for NORIG

- Whenever possible, the clinical center should wait at least 8 weeks after enrollment in the GpR before registering the patient in NORIG. The rationales for this are: (1) we want complete, fresh data in NORIG, and a patient is more likely to be willing to complete forms and procedures if there has been a noticeable duration since he/she completed forms for the GpR; and (2) to encourage patients who are likely NORIG candidates to enter directly into NORIG. The clinical center can use physician discretion regarding registering the patient (i.e., patient can be registered before the suggested 8-week time limit), but this should be the exception rather than the rule
- Have the patient sign the NORIG consent form
- Complete and key the NORIG RG form but do NOT issue a new patient ID number and code
- Blood for biosample repository
 - Whole blood must be collected for plasma banking at the biosample repository even if plasma and serum were already banked for the GpR regardless of the time between enrollment in the GpR and registration in NORIG
- Blood for genetics repository
 - If blood was not already collected for the Genetics Repository, have the patient sign the NORIG genetic consent, collect a sample, and complete the NORIG Blood Collection for DNA (BC) and Genetic Consent Documentation (CG) forms
 - If blood was already collected, do not send another sample unless the yield was unsatisfactory (less than 100 µg)
 - If the yield on the sample drawn when the patient screened for the GpR was satisfactory, leave the GpR BC and CG forms in the data system; the patient does not need to sign the NORIG genetic consent and the NORIG BC and CG forms do NOT need to be completed unless the patient is changing their genetic consent
 - If the yield on the sample drawn when the patient screened for the GpR was unsatisfactory, have the patient sign the NORIG genetic consent form, draw the replacement sample, and complete the NORIG BC and CG forms; the GpR BC and CG forms should remain in the data system

NORIG SOP Part I: Clinical Center Operations**2. Eligibility and enrollment**

- Lab results reported on the GpR Laboratory Results (LR) form may be used on the NORIG LR form if they were obtained within 16 week time window specified on the NORIG LR form. An additional blood draw to obtain magnesium and thyroid stimulating hormone levels may be necessary.
- All interviews and patient questionnaires (baseline history, quality of life, and patient health) must be completed anew for NORIG
- The physical exam (PE) form must be completed anew for NORIG
- If the patient is eventually randomized in NORIG, complete the GpR Closeout (CO) form to suspend the patient's participation in the GpR. You do not need to complete the Missed or Incomplete Visit (MV) form for the missed GpR follow-up visits. The patient remains enrolled in the GpR while participating in NORIG, but the patient is not subject to completion of GpR visits; have the patient complete NORIG follow-up visits and forms
- Retain all GpR forms completed for the patient in the patient's GpCRC file
- Retain the patient's GpR visit windows schedule since it will be needed once the NORIG trial is completed.
- Complete and key the GpR CO form for patients who are enrolled in the Gastroparesis Registry who are subsequently randomized into the NORIG trial. All Registry visits will be due until this form is keyed. The keying of this form will turn off the visit windows for the Gastroparesis Registry.
- Data requirements are not suspended while a patient participates in a GpCRC ancillary study

PPM 27: Transferring patients between studies and the GpR Standard Operating Procedures I, section 6.29 provide additional instructions, but if you cannot find the answer to your question, call or email the Data Coordinating Center.

2.6. Randomization and eligibility checking

Randomization steps

- Complete collection of all required screening data and key all screening data forms within 16 weeks of registration date
- Run electronic check on eligibility (i.e., run the Randomization Task and resolve any missing items or ineligibility conditions)
- Run the Randomization Task and confirm that you want to randomize the patient “now”; this task will officially randomize the patient in NORIG and the randomization assignment and materials needed in follow-up will be generated (i.e., labels, visit time windows); this task will categorize each patient into one of two treatment groups:
 - Nortriptyline 10 mg, one capsule
 - Nortriptyline placebo 10mg, one capsule
- **Complete and key the Drug Dosing Determination and Dispensing (DD) form to receive the bottle number of study drug to be given to the participant**
- **Complete and key the Study Drug Dispensing and Return (RD) form within one hour of dispensing study drug to the participant**

Overriding eligibility criteria

- Requests overriding eligibility criteria must be made in writing (email) to the DCC (direct the request to Aynur Ünalp-Arida). The request must specify the eligibility criteria for which the override is requested. The request must come from the principal investigator of the clinical center.
- The DCC may require agreement to the override from other GpCRC investigators
- Override requests require time to review and the review process will not be shortened; therefore, requests should be submitted at least one week prior to the end of the screening window.

Randomization date

- The date the clinical center runs the Randomization Task and confirms that the patient is to be randomized “now” and the treatment group is assigned.
 - The “time zero” for reckoning the time windows specified on the patient’s NORIG visit time window guide.
-

2.7. Roll over into Gastroparesis Registry after completion of NORIG trial (CO form)

- Patients who complete participation in the NORIG trial should resume participation in the Gastroparesis Registry (GpR) (if previously enrolled in the Registry) or be invited to join the Gastroparesis Registry (if not previously enrolled)
- The NORIG Closeout form should be completed at the f18 visit (or at the close of the f18 visit window) for all patients randomized in NORIG.
- Ask the patient if he/she consents to re-entering or enrolling in the Gastroparesis Registry
- Patients willing to join the Gastroparesis Registry should sign the most recent version of the Gastroparesis Registry informed consent approved by your IRB (follow your institution's IRB guidelines for re-consenting participants previously enrolled in the Gastroparesis Registry).
- Each consenting patient should be scheduled for a Gastroparesis Registry follow-up visit approximately 14 weeks after the date of their NORIG f18 visit. For patients previously enrolled in the Gastroparesis Registry, consult the patient's Gastroparesis Registry visit schedule (time windows guide) generated at their enrollment and schedule the Gastroparesis Registry visit that is open 14 weeks from the date of their NORIG f18 visit. GpR data collection will not resume until 14 weeks after the NORIG f18 visit
- For patients who were not previously enrolled in the Gastroparesis Registry, a new Registry visit schedule (time windows guide) will be automatically generated when the NORIG Closeout form (CO) is keyed into the web-based data system. The new visit schedule will use the NORIG randomization date as the effective date of enrollment into the GpR. Schedule the participant approximately 14 weeks from their NORIG f18 visit for their f032 GpR follow-up visit. GpR data collection will not begin until 14 weeks after the NORIG f18 visit. Certain laboratory values were not requested in the NORIG trial but are part of the screening process for traditional enrollment into the GpR. These values would be useful to capture in NORIG participants electing to participate in GpR. If available or when clinically indicated, please obtain and record on the GpR Laboratory Results (LR) form, the lab values for anti-nuclear antibody (ANA), scleroderma antibody (Scl-70), C-reactive protein (CRP), serum electrophoresis (SPEP), prothrombin time (PT), International Normalized Ratio (INR), partial thromboplastin time (PTT), and hemoglobin A1c (HbA1c). You do not need to complete the GpR Genetic Consent Documentation (CG) or the GpR Blood Collection for DNA (BC) forms for participants that had blood drawn for DNA banking while in the NORIG trial.

2.7. Roll over into Gastroparesis Registry after completion of NORIG (CO form)

- For NORIG participants who decline to participate in the Gastroparesis Registry, inform them that the study results and their treatment assignment will be available to them after the completion of the NORIG trial, i.e., after all participants complete their treatment and trial results are available.
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3. Certification

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3.1. Certification overview of NORIG

What is certification?

- It is an internal (i.e., related to the study) procedure designed to identify the staff responsible for specific data items or data collection procedures or decisions about eligibility
- It is a managerial and quality assurance tool for the study

Who and what does it apply to?

- It applies to:
 - NORIG trial staff
 - Each clinical center
- Certification for the NORIG trial is required before any patient visits or data collection may occur; patients may not begin any screening examinations, sign any consent statements, or complete any study forms until the clinical center has been certified for the study
- More than one staff member may be certified for a role and it is recommended that more than one staff member be certified for a role

Why do we require it?

- Primary purpose is to help assure consistent conduct of the study over time, within and across clinical centers. The conduct of procedures should be similar across patients and in serial testing of the same patient over the duration of follow-up.
- Study procedures may vary from the usual practice of a participating clinical center, but it is important that methods be carried out in the same manner within and across clinical centers.
- It identifies the staff and sites that carry out study procedures and identifies to staff that they and their site are a part of the NORIG trial.
- It provides a mechanism for tracking who collected key data items or made key decisions.
- The certification process may help a clinical center prepare for study activities by presenting the training, facility, and equipment needs in an organized fashion and requiring acquisition or completion of these items before study specific activities may begin.

NORIG certification

- Certification requirements for NORIG will be issued through notification of each clinical center by a numbered Policy and Procedure Memorandum (PPM).
-

3.2. Clinical center certification

General comments

- Each clinical center participating in the NORIG trial must be certified
- Completion of the Clinical Center Certification (CC) form is required
- IRB approval for the NORIG protocol and consents is required

Purpose of clinical center certification

- Provide information regarding how the clinical center will conduct different aspects of the protocol and who will staff the study
- Guide a clinical center through the steps of getting ready for the NORIG trial – provide a checklist of what needs to be in place before patient activities begin

Requirements for certification of a clinical center

- Complete the NORIG Clinical Center Certification (CC) form
 - Certify at least one person for each role that requires certification (a person may be certified for more than one role)
 - Obtain IRB approval of the most current NORIG protocol and consent documents
 - Receive written notice of approval (e-mail) from the Data Coordinating Center
-

3.3. Personnel certification

Staff roles requiring certification

- Clinical Coordinator
- Study Physician
- Data Entry Technician

Requirements

- Everyone
 - Read the NORIG trial protocol and all Standard Operating Procedures
 - Complete the NORIG Knowledge Assessment (KA) form; this is a written general knowledge assessment about the NORIG trial (open book)
 - Complete the NORIG Personnel Certification (PC) form; this form identifies the roles applied for and provides an assurance of data confidentiality and integrity
- Additional requirements for Study Physician
 - Study Physician must be an MD, preferably a gastroenterologist
- Additional requirements for Data Entry Technician
 - Complete the NORIG Data Entry Certification/Decertification Request (DC) form
 - Read SOP III: Web-based data management system
 - Complete the web-based data management system tutorial (personnel previously certified for the Data Entry Technician role do not need to complete the data system tutorial a second time)

Process

- Send required materials to the DCC
- The DCC will send written notice of approval for certification or pending certification
- Each staff member will be issued a Personnel Identification Number (PIN)

Staff PINs

- Each staff member certified for at least one role will be issued a PIN which will consist of 3 digits – the first digit will identify the clinical center and the next two digits will be a sequential number assigned by the Data Coordinating Center
 - The PIN is used when completing forms
 - The Data Entry Technician uses his/her PIN when signing on to the web-based data management system
 - Staff can be certified for more than one role but will have only one PIN
-

NORIG SOP Part I: Clinical Center Operations

4. Human subjects

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4.1. Background

Consent to participation in the Nortriptyline for Idiopathic Gastroparesis (NORIG) trial must be completed before screening for the study may begin. The patient must consent to procedures offered to and performed on him/her for screening, as well as to the follow-up visits which the patient will face in the future.

The consent process is a dynamic process involving explanations, time to think, questions, clarifications, and advice that a patient may seek from relatives, friends or anybody else considered relevant. We wish to inform the prospective participant as much as possible and as accurately as possible about what will be offered to him/her, how it will be done, what are the reasonable risks and benefits, what are the alternatives, and what is expected of the patient. We wish to answer patients' questions in a consistent and complete way.

The NORIG trial consent process has three major stages:

- The patient is asked to consent to screening and randomization into the NORIG trial
- The patient is asked to consent to the collection, storage, and use of blood samples for genetic research
- The patient is asked to sign the HIPAA authorization to disclose protected health information

Once the consent forms have been signed, proceed with the completion of the NORIG Registration (RG) form. At the end of the screening process, the patient is asked to re-affirm their consent on the Randomization (RZ) form.

4.2. Institutional Review Board process

Two template consent statements have been prepared for the Nortriptyline for Idiopathic Gastroparesis (NORIG) trial:

- Consent for screening and enrollment in NORIG
- Consent for the collection, storage, and use of blood samples for current and future genetic research

Clinical centers are expected to use these materials in their submissions to their Institutional Review Boards (IRBs) for approval to participate in the NORIG trial. Each clinic must send copies of the consent statements to be used in their clinic, stamped with their IRB's approval, to the Data Coordinating Center and to the NIDDK Repositories for approval prior to initiating patient activities in the NORIG trial. Data Coordinating Center staff will review and compare each clinical center's approved consents to the template consents. The NIDDK Repository will review each clinical center's consents and issue an approval letter. Once the approval letter is received, the necessary shippers will be sent to the clinical center. Specific local additions to and editing of the templates may be required at individual institutions, but deletion of material and major rewording of text may need to be explained and justified. Once a consent form has been approved by an institution's IRB, it cannot be changed without the IRB's approval.

The study protocol, consent forms, and data collection forms will be submitted to each clinical center's IRB and to the Data Coordinating Center's IRB. Additionally, each clinical center will submit to their IRB any recruitment materials to be used at their site. A clinical center may not initiate any patient contact about the NORIG trial until the site has IRB approval for the NORIG trial and the Data Coordinating Center has certified the site for initiation of patient activities. All study personnel will have completed training in the Protection of Human Subjects per NIH guidelines.

HIPAA authorization forms will be prepared by each clinical center according to local clinical center institutional requirements and guidelines.

4.3. Consent administration

Nortriptyline for Idiopathic Gastroparesis (NORIG) consents

It is assumed that patients referred to a clinical center for screening have heard about the NORIG trial, but their level of knowledge and expectations may well differ. We wish to standardize the consent administration across clinical centers as much as possible. Administration of the NORIG consents involves two tasks:

- (1) A NORIG staff member must sit down with the patient and review the contents of the statement; explain the risks, benefits, and responsibilities of participation; review the alternatives to participation; and answer questions.
- (2) A NORIG certified study physician (i.e., a NORIG certified gastroenterologist) must sign the consent statement, taking overall responsibility for the patient's informed and voluntary consent.

Staff at each clinical center should be designated to carry out these tasks. The rationale for requiring that the consent statement be signed by a study physician is to help assure that the physician signing the consent is one who has a broad role in the study.

Generally, patients should be given the consent statements to read through at least a day before signature is requested. The consent will then be reviewed with the patient by the staff member designated to obtain consent; the consenter may opt to read the statement to the patient, pausing to explain issues as needed. This activity should take place in a quiet, private and relaxed setting in the clinical center.

The patient should sign the consent statement in the presence of the NORIG staff member after all questions have been answered and when the patient has asserted orally that he/she is ready to sign the consent. After the patient has signed and dated the consent, the patient should meet with a NORIG study physician for the physician to sign the consent statement; ordinarily this meeting should take place on the same day that the patient signed the consent statement. The physician should ask the patient to confirm his/her voluntary consent and query the patient about any questions or concerns the patient may have about participation. Both signatures on the consent form must be in a non-erasable ink pen. If the physician cannot meet with the patient on the same day that the patient signs the consent statement, the physician may sign on another day. It is good practice to make an entry in patient's chart that the consent form was discussed and consent was obtained.

Consent for genetic research

The consent for collection and banking of blood for genetic research should be administered in the same way that the NORIG consent is administered, except that it should not be signed until the patient has been determined to be eligible for the NORIG trial.

4.4. Time considerations for obtaining consent

- The **NORIG Consent and HIPAA authorization** must be obtained at the start of the initial screening visit; documents from the referring physician (if any) should have been reviewed prior to the visit and the patient judged eligible for screening prior to the visit. Signature of this consent is required prior to sending the patient for any NORIG trial diagnostic tests. A check for signature of this consent statement occurs on the NORIG Registration (RG) form.
 - The **NORIG Consent for Collection, Storage, and Use of Blood Samples for Current and Future Genetic Research** must be obtained after eligibility for the NORIG trial has been established, during screening. Signature of this consent is required prior to drawing blood for genetic research for the NORIG trial; a check for signature of this consent statement occurs on the NORIG Blood Collection for DNA (BC) form. Signature of this consent statement is not required for NORIG trial eligibility (i.e., the patient may choose not to participate in the genetic research component of the NORIG trial).
 - A patient may be given the consent statements to review prior to the initiation of screening visit to meet patient needs with respect to review time. Whenever a consent is first given to a patient for review, it should be made clear to the patient that the consent should not be signed until requested by a NORIG staff member. The consents may be mailed to the patient prior to screening visit. Whatever timing is used by a clinic, the patient should be allowed enough time to reflect about the proposed NORIG procedures, pose questions, and consult with other individuals that he/she considers relevant to their participation in the NORIG trial. Patients may request and should be given time to "think it over" at home and come back at a later time.
-

4.5. Consent handling

- Signed consent statements are important legal documents. These signed statements should be kept in the patient's NORIG clinical center file together with his/her other NORIG forms and documents. These forms are not part of the individual's institutional medical record, but part of his/her study record in the NORIG trial. Consent statements will be examined during site visits.
 - Consents should be annotated with the patient's study identifiers (ID number and code).
 - The NORIG trial consent statement is an “all or none” form. The patient either accepts it in its entirety and signs it, or does not. The patient must consent to the evaluation procedures, the follow-up evaluations, and the banking of his/her plasma. If the patient refuses any part, the patient may not enroll in the NORIG trial.
 - The NORIG trial Consent for Genetic Research has been made a separate consent statement so that the patient can opt out of genetic research and still participate in the NORIG trial.
-

4.6. Informing participants of changes to consent statement after randomization

As new data become available during the conduct of the NORIG trial, the consent statements may need to be changed to reflect the current assessment of risks and benefits to participants in the trial.

Procedures for dissemination of revisions of consent statements from the DCC

- Changes deemed necessary will be made to the prototype consent statements
- Revisions of the prototype consent statements will be distributed to sites via a numbered Policy and Procedure Memorandum (PPM) with instructions to submit the revised consent to their IRB

Procedures for reviewing changes to consent statements with participants

- Clinical center personnel will develop a chronology of IRB approved changes to the consent statements used at their site
 - At each follow-up visit, staff will use the chronology of consent changes to review with the participant any changes to the consent since the last visit. This review does not require obtaining the participant's signature on a new consent statement, unless the local IRB requires obtaining a signature.
 - Review changes to the consent statements with participants at follow-up visits
 - This review process is not intended to be a reaffirmation of consent. The clinical center, if required by their local IRB, may develop procedures for reaffirmation of consent.
-

4.7. Consenting roll over patients from Gastroparesis Registry

If the patient previously enrolled in the Gastroparesis Registry

- Consent as for a new NORIG patient

If the patient previously consented to DNA banking as part of the Gastroparesis Registry

- Patient does not need to sign new consent for DNA banking as part of NORIG. You do not need to complete the NORIG Genetic Consent Documentation (CG) or the NORIG Blood Collection for DNA (BC) forms for participants that previously consented and had blood drawn for DNA banking while in the Gastroparesis Registry.
-

4.8. HIPAA considerations

Nortriptyline for Idiopathic Gastroparesis (NORIG) study staff have access to patient health information and to patient identifiers, such as name, address, and telephone number. Study records are to be kept in a secure place. Only people working on the NORIG trial should have access to these records. However, these records could be reviewed to make sure that the trial is being done as it should. People who may see medical records supporting study records are:

- Officials of your institution
- Your institution's research ethics committee
- Monitors from the GpCRC Data Coordinating Center at the Johns Hopkins University, or other individuals selected by the GpCRC Steering Committee to monitor the study
- Members of the Data and Safety Monitoring Board (DSMB) to monitor overall progress of the study
- Government officials from the Office of Human Research Protections (OHRP) or the National Institutes of Health (NIH) or the Food and Drug Administration (FDA)

Each clinical center should take steps to protect patient privacy. The assigned patient ID number and code should be used to identify patients on forms and in the data files. Personal information such as name, address, and telephone number should be kept only at the clinical center where a patient completes visits.

People outside the clinical center who will receive NORIG trial data include:

- The GpCRC Data Coordinating Center at the Johns Hopkins University in Baltimore, Maryland (or its successor) to maintain the central study database
- The GpCRC Data and Safety Monitoring Board to review the NORIG data for performance and safety
- The NIDDK Genetics Repository at Rutgers, the State University of New Jersey in New Brunswick, New Jersey (or its successor) will receive patients' blood to obtain DNA; the blood samples for a particular patient will be identified by the patient's study ID number and code, not by name
- The NIDDK Biosample Repository at Fisher Bioservices in Germantown, Maryland (or its successor) will receive patients' plasma; the samples for a particular patient will be identified by the patient's study ID number and code, not by name
- The GpCRC investigators, as well as outside researchers, to analyze and report NORIG trial data. Patient identity will not be disclosed in any reports or publications resulting from the trial. While the NORIG trial is ongoing, the use of the NORIG trial data must be approved by the GpCRC Steering Committee and by the research ethics committee at your institution.

4.8. HIPAA considerations

Patient agreement to enter the NORIG trial indicates that the patient also agrees to the use of the data as described above. If a patient does not agree to the described uses of the data, the patient may not participate in the NORIG trial. The only exception is refusal to provide blood for DNA banking for genetic research; patients may refuse to provide blood for genetic research and still enroll in the NORIG trial.

NORIG SOP Part I: Clinical Center Operations

5. Study visits

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5.1. Overview of visit schedule

The patient-related activities of the NORIG trial can be divided into 4 phases:

- Screening for eligibility (2 visits over a maximum of 16 weeks)
- Randomization to treatment (1 visit and it may be combined with the last screening visit)
- Treatment phase (5 visits over 15 weeks)
- Treatment tapering phase (from weeks 15 to 17 after randomization, last week without study medication, final visit at 18 weeks)

The screening phase may be conducted over 2 or more visits. Clinical centers may alter the order of the visits or modify the procedures done on a particular visit. For example, some centers may elect to perform the EGG and satiety test at the first screening visit or at a second screening visit. The last screening visit may be combined with the randomization visit for the convenience of the participant. The visit schedule is a guide for the centers and allows flexibility in completion of screening procedures, however, a randomization assignment will be issued only if the data system shows that the patient is eligible, has signed the consent statement, and has had all required screening forms keyed to the data system.

Screening (must be completed within 16 weeks of registration date)

- s1: The patient should be in a fasting state (no food or drink after midnight except for 4 oz (120 mL) of water the night before) for this visit. The patient will sign the consent at or prior to screening visit 1 and will undergo a history and physical examination to identify other illness and contraindications for participation such as use of narcotics for pain more than 3 days per week (including fentanyl patches), use of calcium channel blockers, use of erythromycin, use of medications that are strongly anticholinergic, hypersensitivity or allergy to any tricyclic antidepressant drug, concomitant therapy with a monoamine oxidase inhibitor (MAOI), recent myocardial infarction, or glaucoma. The baseline medical history form will have a section called Gastroparesis Symptoms Inventory to establish a baseline symptom profile for each participant and to document non-specific symptoms that may be attributed as side effects to study drug after randomization. The patient will be asked to respond to a battery of questions including the clinical global patient impression (CGPI). Patients will also complete the following questionnaires:
 - Gastrointestinal Symptoms Rating Scale (GSRS)
 - Health-related quality of life questionnaire (SF-36)
 - Beck Depression Inventory (BDI-II)
 - Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM)
 - State Trait Anxiety Inventory (STAI)
 - Brief Pain Inventory (BPI)
 - Patient Health Questionnaire (PHQ-15)

5.1. Overview of visit schedule

Anthropometric assessments (body weight [kg], body height [m], body mass index [BMI], waist circumference [cm], hip circumference [cm], vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature); and general physical findings will be collected and recorded. Patients will have an ECG performed at this visit. Laboratory test results that need to be recorded from chart review or obtained as part of screening include: a complete blood count (CBC): white blood cells, red blood cells, hemoglobin, platelets), a metabolic panel: (sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogen (BUN), creatinine; a hepatic panel: albumin, total protein, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin.

- s2: Patients will return to the clinical center in a fasting state (no food or drink after midnight the night before with the exception of up to 4 oz (120 mL) of water the night before). They will have 10 mL of blood drawn for plasma banking and 20 mL of blood drawn for DNA banking. The DNA banking is for pharmacogenomic analysis of CYP450 2D6 alleles and plasma banking is for measurement of the study drug blood levels centrally. Patients will complete the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM) questionnaire and also undergo a satiety test with electrogastronomy (EGG) as outlined in SOP I, section 6.4.

The last form to be completed at screening should be the Randomization form (RZ) which reaffirms the patient's consent to participate in the NORIG trial.

Randomization

- rz: Women of childbearing potential must have a negative pregnancy test. Randomization occurs when the clinical center staff runs the enrollment task on the web based data management system and the patient is found to be eligible. A randomization assignment will be issued only if the data system shows that the patient is eligible, has signed the consent statement, and has had all required baseline data keyed to the data system.

Once the patient is successfully randomized to the NORIG trial, the Drug Dosing Determination and Dispensing (DD) form must be completed and entered in the web-based data management system to receive the specific numbered medication bottle to be given to the patient. This number is patient specific and will correspond to numbered bottles of medication which have been sent to the clinical center's research pharmacy (or clinical coordinator if not using a pharmacy) by the GpCRC Drug Distribution Center. The research pharmacy (or clinical coordinator) will issue the assigned numbered bottle to the patient. Each patient's random treatment assignment will be generated for that specific patient and will not be transferable to another patient. Once the assignment has been generated, the patient should be issued the assigned study drug (in person) and instructed about when to take the study drug and monitoring for potential adverse effects.

The study drug dispensed at the time of randomization will be either a 10 mg capsule of nortriptyline or a similar looking placebo capsule. Once the study drug is dispensed to the patient, remove the tear-off portions of the label and affix one to your clinical

5.1. Overview of visit schedule

center's drug inventory log and one on the Study Drug Dispensing and Return (RD) form. The RD form must be entered in the data system within one hour of dispensing study drug.

Follow-up

- f03: Obtain a medical history including the gastroparesis symptoms inventory, the global overall relief of symptoms question and clinical global patient impression question. Have the patient complete the following questionnaires: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II). Review study drug adherence and tolerance with the initial 10 mg dose of study drug with patient. Collect any remaining medication bottles with unused study drug. If the 10 mg dose is well tolerated during the first 3 weeks after randomization, dispense study drug with instructions for a 25 mg dose (one 25 mg capsule). The RD form must be entered in the data system within one hour of dispensing study drug.
- f06: Obtain a medical history including the gastroparesis symptoms inventory, the global overall relief of symptoms question and clinical global patient impression question. Have the patient complete the following questionnaires: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II). Review study drug adherence and tolerance with the 25 mg dose of study drug since the week 3 visit with patient. Collect any remaining medication bottles with unused study drug. If the 25 mg dose is well tolerated during weeks 3-6 after randomization, dispense study drug with instructions for a 50 mg dose (two 25 mg capsules). The RD form must be entered in the data system within one hour of dispensing study drug.
- f09: Obtain a medical history including the gastroparesis symptoms inventory, the global overall relief of symptoms question and clinical global patient impression question. Perform a physical exam (temperature, heart rate, respiratory rate, blood pressure). Have the patient complete the following questionnaires: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), a health-related quality of life questionnaire (SF-36), State Trait Anxiety Inventory (STAI), Brief Pain Inventory (BPI), Patient Health Questionnaire (PHQ-15), and Beck Depression Inventory (BDI-II). Once the questionnaires are completed, the patient will have an electrocardiogram (ECG). Review ECG findings, study drug adherence and tolerance with the 50 mg dose of study drug since the week 6 visit with patient. Collect any remaining medication bottles with unused study drug. If the 50 mg dose is well tolerated during weeks 6-9 after randomization, dispense study drug with instructions for a 75 mg dose (three 25 mg capsules). Women of childbearing potential must have a negative pregnancy test. The RD form must be entered in the data system within one hour of dispensing study drug.

5.1. Overview of visit schedule

- f12: Patient should be in a fasting state (no food or drink after midnight the night before with the exception of up to 4 oz (120 mL) of water). Obtain a medical history including the gastroparesis symptoms inventory, the global overall relief of symptoms question and clinical global patient impression question. Perform a physical exam (temperature, heart rate, respiratory rate, blood pressure) and draw 25mL of blood for banking and analysis; 10 mL of blood will be drawn for plasma banking; and 15 mL will be drawn for a complete blood count (white blood cells, red blood cells, hemoglobin, hematocrit, platelets), a metabolic panel (sodium, potassium, chloride, carbon dioxide, calcium, magnesium, blood urea nitrogen (BUN), creatinine, and a hepatic panel (albumin, total protein, alkaline phosphatase, alkaline aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin. Have the patient complete the following questionnaires: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptom Rating Scale (GSRS), and Beck Depression Inventory (BDI-II). Once the questionnaires are completed, the patient will have an electrocardiogram (ECG) followed by the EGG and satiety test. Review ECG findings, study drug adherence and tolerance with the 75 mg dose of study drug since the week 9 visit with patient. Collect any remaining medication bottles with unused study drug. If 75 mg dose is well tolerated during weeks 9-12 after randomization, dispense study drug with instructions for a 75 mg dose (three 25 mg capsules). The RD form must be entered in the data system within one hour of dispensing study drug. Women of childbearing potential must have a negative pregnancy test.
- f15: Patient should be in a fasting state (no food or drink after midnight the night before with the exception of up to 4 oz (120 mL) of water). Obtain a medical history including the gastroparesis symptoms inventory, the global overall relief of symptoms question and clinical global patient impression question. Perform a physical exam (temperature, heart rate, respiratory rate, blood pressure) and draw 10 mL of blood for plasma banking. Have the patient complete the following questionnaires: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), a health-related quality of life questionnaire (SF-36), State Trait Anxiety Inventory (STAI), Brief Pain Inventory (BPI), Patient Health Questionnaire (PHQ-15), and Beck Depression Inventory (BDI-II). Review study drug adherence and tolerance with the 75 mg dose of study drug since the week 12 visit with patient. Collect medication bottles with unused study drug. Patients who reached the 75 mg dose will be instructed to reduce their dosage to 50 mg (two 25 mg capsules) for one week and then to 25 mg (one capsule) the second week and end with one week of no study drug use and return for the final follow-up visit at week 18 (ensure patient has 21 capsules (25 mg) for tapering). Patients who reached the 50 mg dose will be instructed to reduce their dosage to 25 mg for one week and end with two weeks of no study drug use and return for the final follow-up visit at week 18. Patients who were on a maximum dose of 25 mg will be instructed to reduce their dosage to 10 mg for one week and end with two weeks of no study drug use and return for the final follow-up visit at week 18 (dispense a bottle of 10 mg capsules for tapering). The RD form must be entered in the data system within one

NORIG SOP Part I: Clinical Center Operations**5. Study visits**

hour of dispensing study drug. Patients who were on a maximum dose of 10 mg will stop the study drug, no tapering is required. Women of childbearing potential must have a negative pregnancy test.

- f18: Obtain a medical history including the gastroparesis symptoms inventory, the global overall relief of symptoms question and clinical global patient impression question. Have the patient complete the following questionnaires: Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM), Gastrointestinal Symptoms Rating Scale (GSRS), and Beck Depression Inventory (BDI-II). Collect any remaining medication bottles with unused study drug. Key the RD form to document return of all study drug bottles. The Closeout (CO) form should be completed at the f18 visit for all patients randomized in NORIG as outlined in SOP I, section 6.29.
-

5.2. Visits, data forms, and procedures

Phase/ Visit	Form abbr	Procedure
Screening		
s1	RG	Registration (document consent, sociodemographics, assign IDs)
	PL	Patient location (patient contact information)
	BH	Baseline medical history
	PE	Physical exam including electrocardiogram
	EG	Upper endoscopy documentation
	GE	Gastric emptying scintigraphy documentation
	LR	Laboratory results (The following laboratory test results are required to be recorded during screening: hematology, metabolic panel, hepatic panel, and thyroid stimulating hormone)
	GD	Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)
	GS	Gastrointestinal Symptoms Rating Scale
	QF	SF-36 Health Survey
	BD	Beck Depression Inventory
	SE	State-Trait Anxiety Inventory
	PI	Brief Pain Inventory
	PQ	Patient Health Questionnaire
s2	PL	Patient location
	PE	Physical exam (if not performed at s1 visit)
	CG	Genetic consent documentation
	BC	Blood collection for DNA
	BP	Blood processing for plasma
	GP	NIDDK Genetics phlebotomy form
	ST	Electrogastrogram and Satiety Test

The screening phase may be conducted over 1 or 2 visits. Clinical centers may alter the order of the visits or modify the procedures done on a particular visit. For example, some centers may elect to perform the EGG and satiety test at the first screening visit. The last screening visit may be combined with the randomization visit for the convenience of the participant. The visit schedule is a guide for the centers and allows flexibility in completion of screening procedures, however, a randomization assignment will be issued only if the data system shows that the patient is eligible, has signed the consent statement, and has had all required screening forms keyed to the data system.

5.2. Visits, data forms, and procedures

Phase/ Visit	Form abbr	Procedure
Randomization		
rz	PE	Physical exam (required only once during screening)
	RZ	Eligibility check and treatment assignment
	DD	Drug dosing determination and dispensing
	RD	Study drug dispensing and return
	PL	Patient location (update as needed)
Follow-up phase		
<i>The patient should be in a fasting state (no food or drink after midnight the night before with the exception of 4 oz (120 mL) of water) for follow-up visits f12 and f15.</i>		
3 week follow-up visit		
f03	FH	Follow-up medical history
	GD	PAGI-SYM questionnaire
	GS	Gastrointestinal Symptoms Rating Scale
	BD	Beck Depression Inventory
	DD	Drug dosing determination and dispensing
	RD	Study drug dispensing and return
	LR	Laboratory test results will be recorded if available during follow-up
	PL	Patient location (update as needed)
6 week follow-up visit		
f06	FH	Follow-up medical history
	GD	PAGI-SYM questionnaire
	GS	Gastrointestinal Symptoms Rating Scale
	BD	Beck Depression Inventory
	DD	Drug dosing determination and dispensing
	RD	Study drug dispensing and return
	LR	Laboratory test results will be recorded if available during follow-up
	PL	Patient location (update as needed)
9 week follow-up visit		
f09	FH	Follow-up medical history
	PE	Physical exam including electrocardiogram
	GD	Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)
	GS	Gastrointestinal Symptoms Rating Scale

NORIG SOP Part I: Clinical Center Operations

5. Study visits

5.2. Visits, data forms, and procedures

Phase/ Visit	Form abbr	Procedure
	QF	SF-36 Health Survey
	BD	Beck Depression Inventory
	SE	State-Trait Anxiety Inventory
	PI	Brief Pain Inventory
	PQ	Patient Health Questionnaire
	DD	Drug dosing determination and dispensing
	RD	Study drug dispensing and return
	LR	Laboratory test results will be recorded if available during follow-up
	PL	Patient location (update as needed)
12 week follow-up visit		
f12	FH	Follow-up medical history
	PE	Physical examination including electrocardiogram
	BP	Blood processing for plasma
	GD	PAGI-SYM questionnaire
	GS	Gastrointestinal Symptoms Rating Scale
	BD	Beck Depression Inventory
	ST	Electrogastrogram and Satiety Test
	DD	Drug dosing determination and dispensing
	RD	Study drug dispensing and return
	LR	Laboratory test results for hematology, metabolic panel and hepatic panel are required at f12
	PL	Patient location (update as needed)
15 week follow-up visit		
f15	FH	Follow-up medical history
	PE	Physical examination
	BP	Blood processing for plasma
	GD	PAGI-SYM questionnaire
	GS	Gastrointestinal Symptoms Rating Scale
	QF	SF-36 Health Survey
	BD	Beck Depression Inventory
	SE	State-Trait Anxiety Inventory
	PI	Brief Pain Inventory
	PQ	Patient Health Questionnaire
	DD	Drug dosing determination and dispensing
	RD	Study drug dispensing and return
	LR	Laboratory test results will be recorded if available during follow-up
	PL	Patient location (update as needed)

NORIG SOP Part I: Clinical Center Operations

5. Study visits

5.2. Visits, data forms, and procedures

Phase/ Visit	Form abbr	Procedure
18 week follow-up visit		
fl8	FH	Follow-up medical history
	GD	PAGI-SYM questionnaire
	GS	Gastrointestinal Symptoms Rating Scale
	BD	Beck Depression Inventory
	RD	Study drug return
	LR	Laboratory test results will be recorded if available during follow-up
	PL	Patient location (update so study results can be mailed at a later date)
	CO	Closeout form

5.3. Guide for screening visit s1

The screening visits may be conducted over 1 or 2 visits. Clinical centers may alter the order of the visits or modify the procedures done on a particular visit to meet their needs. The last screening visit may be combined with the randomization visit for the convenience of the participant. This visit guide allows flexibility in completion of screening procedures, however, a randomization assignment will be issued only if the data system shows that the patient is eligible, has signed the consent statement, and has had all required screening forms keyed to the data system.

Procedures

- Obtain signed consent for the NORIG trial (consent form and HIPAA authorization form)
- Obtain permission to abstract data from patient's medical records
- Obtain patient location information
- Initiate data collection for screening and baseline values
 - Physical exam and anthropometric measurements (height, weight, waist circumference, hip circumference, temperature, blood pressure, resting radial pulse, respiratory rate, electrocardiogram)
 - Interview for baseline medical history (responses may be modified or expanded upon chart review)
 - Laboratory testing (hematology, metabolic panel, hepatic panel, thyroid stimulating hormone)
 - Upper endoscopy results documentation
 - Gastric emptying scintigraphy results documentation
 - Questionnaires regarding gastroparesis symptom severity, quality of life, pain, and depression
- If patient appears eligible at the close of visit s1
 - Schedule patient for visit s2
 - Schedule patient for any needed tests

Data collection forms

- Forms completed for all patients
 - RG Registration (document consent, sociodemographics, assign IDs)
 - PL Patient Location (patient contact information)
 - BH Baseline Medical History
 - PE Physical Examination with electrocardiogram
 - EG Upper Endoscopy Documentation
 - GE Gastric Emptying Scintigraphy Documentation
 - LR Laboratory Results (completion of all laboratory test results required during screening: hematology, metabolic panel, hepatic panel, and thyroid stimulating hormone)
 - GD Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)
 - GS Gastrointestinal Symptoms Rating Scale

5.3. Guide for visit s1

- QF SF-36 Health Survey
- BD Beck Depression Inventory
- SE State-Trait Anxiety Inventory
- PI Brief Pain Inventory
- PQ Patient Health Questionnaire

Forms for clinical center use only

- PL - Patient Location
- Medical records release (use local form)

Before the patient leaves the clinical center

- Register patient on clinic data system

After the patient leaves the clinical center

- Key completed data forms
 - Set up a NORIG trial chart for patient and file the completed forms.
-

5.4. Guide for visit s2

The screening visits may be conducted over 1 or 2 visits. Clinical centers may alter the order of the visits or modify the procedures done on a particular visit to meet their needs. The last screening visit may be combined with the randomization visit for the convenience of the participant.

Before the patient arrives for the visit

- Abstract data from patient's medical records as needed
- Apply preprinted MACO labels to forms as appropriate
- Gather blood collection and mailing materials (labels, tubes, shippers)
- If advisable, alert phlebotomy lab staff of need to obtain plasma samples
- Confirm eligibility with respect to whatever data have been keyed
- Prepare EGG and satiety test materials

Procedures

- Obtain consent for DNA banking (if available)
- Collect blood for genetic (DNA) banking (2 tubes) and plasma banking (1 tube)
- Complete EGG with satiety test
- Confirm eligibility (hand/eyeball review of unkeyed data)
- Explain to the patient that you will electronically confirm eligibility after keying the data collected at this visit but that since you believe the patient to be eligible, you would like to schedule the patient for the randomization visit

Data collection forms (form abbreviation)

- Forms completed for all patients
 - CG - Genetic Consent Documentation (this form documents both consent and refusal)
 - BP - Blood Processing for Plasma
 - ST - Electrogastrogram and Satiety Test
- Additional forms for patients who consent to blood draw for DNA extraction
 - BC - Blood Collection for DNA
 - GP - NIDDK Genetics Phlebotomy form

Forms for clinical center use only

- Check for updates to Patient Location (PL)

After the patient leaves the clinical center

- Ship whole blood specimen for DNA extraction to NIDDK Genetics Repository at ambient temperature by overnight Fed Ex delivery service. Shipments may be sent to the Genetics Repository Monday-Friday.
 - Process blood to plasma aliquots for banking; store in local freezer at -70° until a batch sufficient for shipping accumulates or one month passes
 - Key data collection forms
 - Run Randomization Task and re-check eligibility
-

5.5. Randomization visit

Procedures

- Randomization visit may be combined with the last screening visit.
- Requests for randomizations will be made by clinical centers using the web based data management system.
- A randomization assignment will be issued only if the database shows that the patient is eligible, has signed the consent statement, has had all required baseline data keyed to the database and the clinical center staff indicate they wish to randomize the patient.
- Once patient is successfully randomized into the NORIG trial, you must complete and enter the Drug Dosing Determination and Dispensing (DD) form into the web based data management system to receive the specific numbered medication bottle of 10 mg nortriptyline or placebo assigned to the patient
- Patient is given the assigned study drug bottle with a number unique to the patient, instructed about starting the drug and monitoring for adverse effects, and begins taking study drug.
- Once the study drug is dispensed to the patient, remove the tear-off portions of the label and affix one to your clinical center's drug inventory log and one on the Study Drug Dispensing and Return (RD) form. The RD form should be entered in the data system within one hour of dispensing study drug.

Data Collection Forms

- RZ - Randomization checklist
- DD - Drug Dosing Determination and Dispensing
- RD - Study Drug Dispensing and Return

(These data collection forms must be keyed into the data system in this order)

Comment

- The date of randomization visit is the date for reckoning all follow-up visits
 - Use visit windows guide generated at randomization to schedule the first follow-up visit and prepare forms and labels that will be used at visit f03. The f03 visit may not be scheduled sooner than 2 weeks (14 days) after randomization.
-

5.6. Visit windows: randomization and follow-up

- **Randomization** must occur within 16 weeks (112 days) of registration date
 - **f03:** window runs from week 2 through 4 weeks, ideal date is 3 weeks (21 days) after randomization date
 - **f06:** window runs from (4 weeks+1 day) through 7 weeks, must be at least 1 week after f03; ideal date is 6 weeks (42 days) after randomization date
 - **f09:** window runs from (7 weeks+1 day) through 10 weeks, must be at least 1 week after f06; ideal date is 9 weeks (63 days) after randomization date
 - **f12:** window runs from (10 weeks+1 day) through 13 weeks, must be at least 1 week after f09; ideal date is 12 weeks (84 days) after randomization date
 - **f15:** window runs from (13 weeks+1 day) through 17 weeks, must be at least 1 week after f012; ideal date is 15 weeks (105 days) after randomization date
 - **f18:** window runs from (15 weeks+1 day) through 20 weeks, must be at least 1 week after f015; ideal date is 18 weeks (126 days) after randomization
-

5.7. Interim (unscheduled) visits or telephone contacts

- Unscheduled visits or telephone contacts may occur as needed. No time windows or minimum time separations are imposed for such visits or contacts.
 - Data are not collected at interim visits (i.e., data forms are not completed) unless reporting an exacerbation of gastroparesis symptoms, study drug side effects, death or a serious adverse event.
 - If gastroparesis symptom exacerbations or study drug side effects occur for a NORIG trial participant between scheduled NORIG trial visits, complete the Interim Event Report (IE) form;
 - The IE form is used to document (1) events that impact on the patient's treatment or participation in NORIG (e.g., temporary interruption or permanent cessation of study medication), or (2) adverse events thought to be associated with study drug that do not meet the criteria for Serious Adverse Event/IND Safety Report (SR) form, or (3) other event that clinical center staff feel should be reported now rather than wait until the next follow-up visit and that is not recorded on another NORIG form. Adverse events associated with NORIG study medication that are both serious and unexpected should not be reported on this (IE) form, but should be recorded on the IND Safety Report (SR) form.
 - Use visit code n even if reporting an event discovered during a regular follow-up visit. If more than one event is reported on the same calendar day (i.e., same date in item 4 for all events), use visit code n for first event, n1 for second event.
 - Complete and key the IE form for any event that meets the criteria above. The short name (item 21) and the severity code (item 22) are to be obtained from the NCI's Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE document is available at www.gpcrc.us under Documents. Fax the DCC (Attention: Mika Green) (1) a copy of this form; (2) A narrative description of the event; (3) A copy of your report to your IRB if severity grade is 3 or higher (Fax 410-955-0932).
-

NORIG SOP Part I: Clinical Center Operations

6. Study procedures

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6.1. Assignment of study identifiers

What

- The GpCRC uses 2 identifiers for patients
 - ID number (4 digits)
 - ID code (3 alphabetic characters)
- These identifiers help assure confidentiality of patient identity

Materials

- ID number and code labels received from the Data Coordinating Center
- Registration (RG) form

When

- Screening visit 1 (s1)

By whom

- Clinical Coordinator

Procedures

- Complete the NORIG Registration (RG) form; if the patient remains eligible at the close of the form, assign the ID number and code by peeling a label off the label sheet and affixing it to the specified item on form RG or note ID assigned previously in GpCRC (For GpCRC participants registering for NORIG do not assign new ID, use the ID assigned in GpR)
- The patient will be known by these IDs for the duration of the GpCRC, including participation in any other GpCRC studies
- Key the Registration (RG) form into NORIG web-based data management system; this must be the first form keyed and **no other forms may pre-date the date of the RG form**
- The Registration (RG) form should be keyed for each patient screened for NORIG, including patients already enrolled in the Gastroparesis Registry

Comments

- Once an ID number and its associated ID code are assigned, these IDs must be used by the patient for the duration of the GpCRC and cannot be changed
 - Do NOT reassign or reuse IDs assigned to patients found to be ineligible or who refuse enrollment
-

6.2. Screening Contact Log (SL form)

What

- Screening Contact Log

Purpose

- To record information on patients who are contacted as prospective participants for NORIG

When

- Record prospective participants contacted regarding consenting and registration each week

Procedure

- Document your contact with each prospective participant on a single line of the Screening Contact Log (SL) form
 - Each line should be numbered sequentially and the patient identifier may be a name or chart number (this information is not keyed to the data system)
 - Complete items a-k for every prospective participant contacted
 - Number the Screening Contact Log (SL) forms in sequential order
 - Weekly or once you have filled a Screening Contact Log form please key the entire form to the web-based data management system.
 - Key any partial forms during the last week of each month to ensure that your clinical center's recruitment efforts may be summarized accurately in the monthly performance reports
 - Retain the SL forms in your clinical center's NORIG files along with other study forms
-

6.3. Gastric emptying scintigraphy (GE form)

Egg Beaters Gastric Emptying Scintigraphy

The standard scintigraphy meal will consist of a low fat Egg Beaters meal radiolabelled with 0.5 -1 mCi 99Tc; which is scrambled and cooked. This is served with 2 pieces of toast, jam, and water. The meal has a caloric value of 255 kcal (nutritional composition: 72% carbohydrate, 24% protein, 2% fat, and 2% fiber).

Items needed for Egg Beaters Gastric Emptying Scintigraphy

Egg Beaters (egg substitute): 99% real eggs, cholesterol free, fat free, low calorie
 (120 g Egg Beater, 60 kcal, approx two large eggs)
 2 slices of bread (120 kcal),
 Strawberry jam (30 g, 74 kcal)
 Water (120 ml).
 Technetium-99m 0.5 -1 mCi

Gastric emptying studies are generally performed in the morning. Patient should be fasting overnight or for at least 6 hours. (It is all right for the patient to have taken medications with up 4 oz (120 mL of water on arising). Patients should generally stop medications that can affect gastric emptying for 3 days prior to the test. This includes prokinetic agents, narcotic analgesics, and anticholinergic agents.

To prepare the meal, the Egg Beaters is poured into a bowl, sprinkled with 0.5 - 1 mCi 99Tc sulfur-colloid marker on top, mixed, and cooked in a microwave. Alternative is to use a skillet (nonstick frying pan). The Egg Beater mixture is stirred once or twice during cooking and is cooked until it has the consistency of an omelet (3-5 min). The bread is toasted. Jelly is spread on the bread, and a sandwich is made of the jellied bread and cooked egg mixture. The subject completes the sandwich meal within 10 minutes. The staff technologist records how long it takes the subject to consume the meal, the amount of the meal and the amount of water they consume.

Immediately after meal ingestion, the subject will be placed in front of a gamma camera with images taken in the 140 keV 99Tc peak with a 20% window (140 keV \pm 10%). 1 minute of anterior and 1 minute of posterior measurements will be taken. Subsequent images are taken at 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours after meal ingestion and times of the images should be recorded (The 30 minute and 3 hour time points are optional, but should be obtained if possible. The 0 minutes, 1, 2, and 4 hour time points are required for NORIG trial randomization.) In the time between images, subjects can be sitting, standing, or walking but should remain in close proximity to the nuclear medicine section.

6.3. GE form

Analysis is performed using the geometric mean of the anterior and posterior images for each time point which are then corrected for decay. Results are expressed as percent remaining in the stomach.

Gastric Emptying Scintigraphy Documentation (GE form)

- The Gastric Emptying Scintigraphy Documentation (GE) form is used to record results from a gastric emptying scintigraphy to determine eligibility for the NORIG trial.
 - Complete the GE form at screening visit s1 or s2.
 - The gastric emptying scintigraphy must have been performed at a NORIG clinical center within 2 year priors to registration or during screening.
 - Any necessary information not contained in the report (amount of meal or water consumed, time to consume meal) should be gathered from the patient or technician immediately after the test.
 - The Study Physcian should complete the GE form using the gastric emptying scintigraphy report.
 - If patient has had a gastric emptying procedure since the last study visit, results should be recorded on this form using visit code "n".
 - A copy of the scintigraphy report should be attached to the GE form as the source document.
-

6.4. Upper Endoscopy Documentation (EG form)

Purpose

- To document the results of the upper gastrointestinal endoscopy to determine NORIG patient eligibility

When

- Screening visit s1 or s2 (the upper gastrointestinal endoscopy must have been performed within 2 years prior to the registration date)
- As needed during follow-up

Procedure

- Study Physician or Clinical Coordinator completes the form using the available reports (surgical and histology) of the upper gastrointestinal endoscopy procedure
 -
 - The EG form should be completed using the available reports of the upper gastrointestinal endoscopy procedure. Upper gastrointestinal and Endoscopy with Ultrasound (EUS) reports may be used if all of the required components of the EGD are available. Attach a copy of the available GI procedure reports as the source document.
 - If a **Caution** is checked for any item, further review is necessary by the study physician who will determine whether the diagnosis or condition in the Caution item renders the patient ineligible for the NORIG trial.
 - If a **Stop** or **Ineligible** is checked for any item, the patient is ineligible for the NORIG trial unless the item can be resolved within the 112 day screening window (i.e., re-scheduling an EGD).
 - The EG form **can not be keyed to the data system** if there are any Stop or Ineligible items present.
 - The form should be retained in a study file for further evaluation as appropriate or in the file for ineligible patients. Attach a copy of the endoscopy report as the source document.
-

6.5. Electrogastrogram and Satiety Test (ST form)

Pre-test procedures

The patient should fast after midnight the night before the test (nothing to eat or drink except for 4 oz (120 mL) of water the night before). The patient is generally scheduled for a morning appointment at about 8 am for the electrogastrogram (EGG) and satiety test. The EGG will be performed using 3CPM equipment. For each EGG study, the clinical center needs to have:

- At least 4 cans of regular vanilla Ensure® (lactose free) available and refrigerated for each subject. Each can is regular vanilla Ensure® (lactose free) 8 fluid ounces; 237 mL, 250 calories
- A cup that has a 150 mL measured mark for the Ensure®.
- 3 EGG leads
- A dedicated quiet area for the EGG recording
- A reclining chair
- A blanket
- Metric ruler
- 3CPM EGG equipment

Test protocol

On the morning of the EGG and satiety test, the patient will arrive fasting, that is, nothing to eat or drink except for 4 oz of water after midnight the night before the test. Subjects may take their usual medications with a small amount of water (up to 4 oz) up to two hours prior to the study, but should refrain from coffee, tea, or juice.

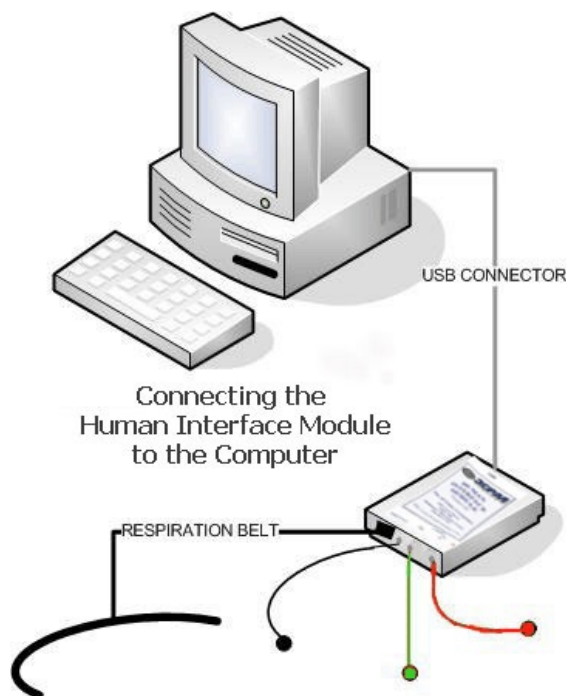
At the time of the visit, the NORIG trial questionnaires and physical examination should be performed first, prior to the EGG and satiety test. Patient should be weighed. The patient should be given the opportunity to use the bathroom. Take the Ensure® out of the refrigerator just prior to starting the EGG baseline recording.

Electrogastrography is the recording of the electrical activity of the smooth muscle, nerves, and interstitial cells, in the stomach using electrodes similar to those used to record the electrocardiogram (ECG). EGG electrodes are placed on the abdominal skin. Skin preparation for these electrodes will consist of cleaning the skin and then applying pre-gelled electrodes. If needed, the abdominal surface where electrodes will be positioned is shaved. The recording is performed in a quiet room with the subject reclining at a 45 degree angle.

6.5. EGG with satiety testing (ST form)

The following practical points will help to ensure a quality EGG recording:

- Record the EGG in a quiet room with subdued light
- Avoid all loud noises or distracting voices
- Position the patient in a comfortable chair or recliner (offer a blanket)
- Instruct the subject to keep arms and legs still, and to avoid any quick body movements.
- Talking should be avoided during the recording. Should an event such as coughing, movement, nausea, talking, etc happen during the baseline or post-stimulation periods of the EGG recording; you can mark the event by placing the mouse cursor over the desired minutes on the EGG tracing (the cursor will change to a pointer finger) and click the left mouse button. A screen will appear that gives you options for marking the event (cough, movement, etc) and a description box if you would like to record something other than the selections available. Once you select or enter the event, choose the "OK" button to complete the recording of the event. You may record an event as many times as one occurs. The object should be to have as many 4 minute segments without any events, so use the event recording only in cases of severe changes in the EGG tracing.

Equipment set-up:


6.5. EGG with satiety testing (ST form)
Technique for skin preparation and electrode placement

1. Prepare to position the EGG electrodes as shown in the 3CPM User Manual:
 - The RED EGG lead wire and electrode (+) is placed on the left mid-clavicular line (left side) approximately two inches below the left costochondral margin (lower ribs).
 - The BLACK EGG lead wire and electrode (-) is placed approximately midway between the xiphoid process and the umbilicus, along the line from the xyphoid process to the umbilicus
 - The GREEN EGG lead wire and electrode (ground) is placed is placed two inches below the right costochondral margin (lower ribs) along the right midclavicular line.
2. Preparing the skin
 - Shave off abdominal hair that is present in these locations for electrodes 1, 2, and 3.
 - Gently abrade the skin in the areas of the electrode positions using a course cloth, 4x4 gauze, or "Buff-Puff".
3. Positioning the electrodes on the skin
 - a) Connect the color-coded EGG lead wires to the Human Interface Module, by matching the lead wire color to the corresponding color-coded plug-in as designated on the Module label.
 - b) Attach the pre-jelled electrodes to the snap-on ends of the EGG lead wires.
 - c) Remove the plastic covers from the adhesive side of the electrode, and place on the skin according to the instructions in #1 above.
4. Positioning and connecting the belt for recording respiration rate

The subject should be in the recording reclining chair at a 45 degree angle which is comfortable for the subject. Attach the belt across the upper chest with the belt clip placed under the armpits and the entire belt pulled snugly to obtain the clearest respiration signal. Check the EGG leads to verify that they are well adhered to the skin before starting the EGG recording.

 - Baseline symptoms prior to EGG recording will be obtained using visual analog scales for stomach fullness, hunger, nausea, bloating, and abdominal discomfort.
 - The subject will mark each symptom line with a vertical line to indicate how they currently feel in terms of that symptom.

6.5. EGG with satiety testing (ST form)

You may elect to start a study for a new patient in one of two ways:

- Select the icon for a new file, from the toolbar just under the top menu.
- Select File from the top menu, then select *New Study*, and then select *New Patient*.

De-identifying patient data:

- For EGG recordings in the NORIG trial, do not enter patient addresses, phone numbers, or social security numbers into the Patient Demographics screen. This will prevent protected health information (PHI) from being displayed, printed, or transferred to Dr. Kenneth Koch at Wake Forest University or the DCC for central reading. It is the responsibility of the clinical center staff to ensure that system protections are utilized to meet HIPAA requirements followed at your institution and implemented by the Gastroparesis Clinical Research Consortium Steering Committee.

The screenshot shows a 'Patient Demographics' window with the following fields and labels:

- Patient Name:** First Name (labeled A), Middle Initial, Last Name (labeled B).
- Date of Birth:** (mm/dd/yyyy)
- Social Security Number:**
- Address:** (labeled C), followed by a second Address field.
- City:**
- State:** and **Zip Code:**
- Phone number:**
- Hospital number:**
- Research reference number:** (labeled D and E).

Buttons at the bottom: Save and Close, Continue, Cancel, and Help.

- Do not follow the guidelines outlined in the 3CPM User Manual for entering patient demographic for NORIG trial research purposes. Instead, enter the participant's information as shown in the figure below:

6.5. EGG with satiety testing (ST form)

- A. Enter the GpCRC 4-digit ID number in the **First Name** field (i.e., 9000)
- B. Enter the 3-letter patient ID code in the **Last Name** field, followed by the visit code(i.e., zzzs1; zzzf12)
- C. Enter the study name in the **Address** field (i.e., NORIG etc.).
- D. Always check the **Research Reference Number** box.
- E. Re-enter the GpCRC 4-digit ID and the 3-letter patient code separated by a hyphen , followed by the visit code (i.e., 9000-zzzf12 for the f12 visit).

Once the demographics have been entered, click on **Continue** to continue with the study.

Cancel stops the study without saving any information.

Save and Close saves the patient demographics and ends the study. The patient won't be available if you try to select a patient study as there is no study yet. However, if at a later date, you start a study again with this patient, the program allows you to use the previously entered patient demographics.

When **Continue** is selected, you may then enter pre-study information.

Equipment test

This section of the study makes sure that the signals (EGG and Respiration) are stable. Both signals must be stable for 2 minutes. The initial screen shows the Respiratory sensor and Gastric electrodes in large red dots. When these turn green, the system is ready to start the baseline recording. The EGG signal, shown in red is in the top graph. The Respiration signal, shown in black is in the bottom graph.

To start the equipment test, select the **Start Equipment Test** button. When both the Respiratory sensor and the Gastric electrodes turn green, the **Begin Baseline** button gets enabled. Then to start the Baseline, select this button.

Recording of EGG and respiratory signals

- If you have not yet removed the Ensure[®] from the refrigerator, remove it now, prior to the 15 minute baseline recording period.
- Allow 2-3 minutes before initiating the study in order to establish a stable skin-to-electrode interface. Obtain the first set of baseline symptoms using the symptoms score sheet (visual analog scale) page 2 of the EGG and Satiety Test (ST) form.

6.5. EGG with satiety testing (ST form)

- Once the EGG and respiratory signals are stable, the baseline (pre-prandial) EGG recording period can begin.
- Patients will undergo a 15 minute baseline EGG in a reclining chair with the subject positioned at a 30-45 degree tilt, which is comfortable for the subject.
 - Select the **Start Baseline** button to start the baseline part of the study. The baseline period should last at least 15 minutes. Once the 15 minutes (baseline) have been reached, select the **Stop Baseline** button. You will then give the patient the symptoms score sheet (ST form page 3) to complete. You will have the options to select **Pause Study, Skip Stimulation, and Stimulation Medium**. You will **always** select the **Stimulation Medium** button and leave this box open during the satiety test. When the subject has completed the satiety test, you will enter the amount of Ensure® consumed in this box.

Satiety test

Patients will begin the Satiety Test. For this, subjects will sit up. During the test, subjects will drink regular vanilla Ensure® (1.1 kcal/mL) at a rate of 150 mL every 5 minutes until they feel "**completely full**." The patient's symptoms are recorded every 5 minutes and the total volume of Ensure® consumed will be recorded on page 6 of the ST form.

Instructions to patients for Satiety Test are as follows:

"You will be given a cup of Ensure® to drink every 5 minutes until you feel completely full. You will have up to 5 minutes to drink each cup. You may use all of this time, if needed. After each drink, we will ask about your feeling of fullness on a five-point scale, that is 0, 1, 2, 3, 4, 5 where 0 is not full at all and 5 is completely full. You will stop drinking when you become completely full from the Ensure®. This is not a test to see how much you can drink, but simply to have you drink until you feel completely full."

- After the subject feels completely full, have them complete the symptoms score sheet on page 5 of the ST form. The total volume of Ensure® consumed (ST form page 4) will be entered into the "stimulation medium" box at this time.
- The subject returns to the same 30-45 degree position that they were in for the fasting baseline condition.
- The electrodes should be checked to verify that they are well adhered to the skin before starting the EGG recording for the 30 minute post satiety period (after the drink is completed). The respiratory belt should be checked to verify it is snug.

6.5. EGG with satiety testing (ST form)
Starting the EGG study recording (post satiety testing)

Once you have entered the amount of Ensure[®] that was consumed (in the *Stimulation Medium box*) you will have two options: the **Start Study** and the **Cancel** button. You will always select the button "Start Study. You will then select the **Begin Study** button; this will start the 30 minute post satiety EGG recording.

- A continuous 30 minute EGG recording is then obtained.
- At the end of the 0-15 minute period, you will have the subject complete a symptoms score sheet (ST form page 6). **Do not select the Finish button** in order for the subject to complete the symptoms score sheet; the EGG should continue to run during this period. At the end of the 16-30 minute postprandial period, you will have the subject complete a symptoms score sheet (ST form page 7). Select the **Finished** button. A check box will appear and you will check the **"Finish the Study"** box and then select the **"OK"** button. Once the study is complete, **save it immediately**. To save the study, click on the icon for saving a file. You can also select **File** from the top menu and then select **Save Patient**. When the study is complete, the raw EGG and respiration signals are displayed for the baseline period. Any events that have been marked are also displayed.
- The electrodes will be removed at this time. This concludes the study.

Selecting minutes for your report:

Once the study is finished you will select good minutes for the Baseline part of the study first. To do this enter the full 15 minute baseline in the box **"Select the Length"** by making the Start Period 0.0 and the End Period 15.0. Once these numbers are entered then check the **Set Period Length** check box. You will then enter into the second set of boxes the artifact free **Start minute** and **End Minutes**. (Example: 4.0 start minute and 14.0 end minute) Once the minutes are entered, you will check the **Set Good Minutes** check box.

Now you can go to the post baseline period, which is after the patient ingested the stimulation medium (Ensure[®]). You can do this by using one of the 4 following methods.

1. Select the go to next period icon, at the top of the screen.
2. Select **Go to** from the top menu and then select **Next period**.
3. Select **Analyze** from the top menu and then select **Post stimulation period 1**. While in this menu item (if you have completed analyzing the baseline period), you will notice that there is a check mark next to the **Baseline period** menu item. This indicates that the baseline period has been analyzed.
4. Open the pull-down list at the top of the screen and select **Post stimulation period 1**. Select the length of the initial period for analysis (minutes 0-15), by setting the **Start minute** and **End minute**.

6.5. EGG with satiety testing (ST form)

NOTICE: The first post stimulation period includes all the minutes of the study (0.0 Start Minute and 30.0 End minute). You will change this and select the length of the first 0 to 15 minute period by making the Start Period 0.0 and the End Period 15.0 then check the ***Set Period Length*** check box. The remaining minutes (after the last minute in the period) will create the second post stimulation period (minutes 16-30). **Do not select more than 15 minutes for any period length.**

Select the artifact free good minutes within the period just created by setting the ***Start minute*** and ***End Minutes***. Choose whole minutes only. Choose **at least 4** consecutive good minutes, up to 15 minutes. Enter the artifact free minutes into the select Start and End boxes and then check the ***Set Good Minutes*** check box.

This same procedure (***Post Stimulation Period 2***) is used for selecting the period length for the remaining minutes 16.0-30.0 and for selecting good minutes. Use the EGG report to complete page 8 of the ST form.

Electrogastrogram and Satiety Test (ST form)

The Electrogastrogram and Satiety Test (ST) form is used to document symptoms and results of the satiety test and electrogastrogram in NORIG trial participants.

- Complete the ST form during screening (s1 or s2) and at follow-up visit f12.
- Have the patient respond to symptom evaluations on pages 2-7 by marking a vertical line in each of the visual analog scales on pages 2, 3, 5, 6, and 7. The scales are 100 mm in length and should be measured from left to right with a metric (SI) ruler. Enter the value closest to the patient's vertical line in millimeters (0-100 mm) in items 9, 10, 14, 15, and 16.
- Using the EGG report, complete section **E. EGG data**
- The Study Physician and Clinical Coordinator should complete section **F. Administrative information**

Best practices when performing the EGG:

- When selecting minutes: choose whole minutes only; choose **at least 4** consecutive good minutes, up to 15 minutes. Do not select more than 15 minutes for any period.
- Attach a copy of the EGG report to the ST form. Save the raw digital EGG data to a USB flash drive.
- EGG and satiety tests should immediately be saved in at least two locations (1) EGG machine's hard drive and (2) the back-up USB drive provided.
- Web support from 3CPM: http://www.3cpmcompany.com/Product_Support1.htm is now used by 3CPM to track support requests from the individual centers. Each person performing EGG's should create an account on the web support page.

Exporting the EGG files:

The 3CPM Export Manual and an updated EGGSAS Research User manual are posted to the GpCRC website. From the home page www.gpcrc.us, click on Documents, then click on *Electrogastrography* and the last bullet is the Export manual.

6.5. EGG with satiety testing (ST form)

The export program does not create a location to hold the exported files. Instead it points by default to the 3CPM folder itself. You must create a folder to export to each time you do an export. Please create a master folder called “NORIG Exported Data”, then create individual subfolders each time you export a group of patient EGG files. This will organize and archive exported NORIG patient data to a specific folder in a way that the data may be tracked and documented. For quality assurance purposes, each clinical center must forward their first two NORIG EGG with satiety test recordings to Wake Forest University for review by Dr. Kenneth Koch. These EGG recordings should be de-identified (see prior EGG PPM 26: Certification for electrogastrography (EGG) and satiety testing in NORIG), do not enter any patient demographics when prompted. Enter the 4-digit patient ID number under **First Name** and the 3-letter patient code in the **Last Name** field. Follow the directions outlined in section 2.2 of the 3CPM EGGSAS Export program manual to select the studies you wish to export to the “NORIG Exported Data” folder.

The EGG file (.egg) and the database file (.mdb) should be emailed to Wake Forest University, to the attention of Judy Hooker (jhooker@wfubmc.edu), Dr. Kenneth Koch (kkoch@wfubmc.edu). Please copy at least two people from the data coordinating center on the email. If you are unable to email the files, you may send the USB drive to Wake Forest at the address below and they will return the USB flash drive to you once the EGG files are copied.

Judy Hooker/Kenneth Koch, MD
 Department of Internal Medicine/Gastroenterology
 Wake Forest University Health Sciences
 Medical Center Boulevard
 Winston-Salem, NC 27157

6.6. Baseline Medical History (BH form)

Who

- Complete for all NORIG patients
- Study Physician and Clinical Coordinator sign the form

What

- The form queries:
 - Symptoms of gastroparesis
 - Medical history (answer items based on information from all sources available to you)
 - Medication used currently and in the past month
 - Baseline non-specific symptom profile and the clinical global patient impression

When

- Screening visit s1 or s2

How

- Mix of interview data and data obtained by chart review
 - Other questions on the BH form can be answered by interview with the patient – i.e., use all sources to get the most accurate information that you can
 - Apply a preprinted MACO label to the last page, Gastroparesis Symptoms Inventory and give to the patient for completion
 - Clinical coordinator should check the returned page for completeness before the patient leaves the clinical center
 - If a **Caution** is checked for any item, further review is necessary by the study physician who will determine whether the diagnosis or condition in the Caution item renders the patient ineligible for or unlikely to comply with the requirements of the NORIG trial.
 - If a **Stop** or **Ineligible** is checked for any item, the patient is ineligible for the NORIG trial unless the item can be resolved within the 112 day screening window (gastroparesis symptom duration is less than 6 months, medication use will be stopped for a washout period).
 - The BH form **can not be keyed to the data** system if there are any Stop or Ineligible items present
 - The form should be retained in a study file for further evaluation as appropriate.
-

6.7. Follow-up Medical History (FH form)

Who

- Complete for all NORIG patients
- Study Physician and Clinical Coordinator sign the form

What

- The form queries/reviews
 - Change in patient's symptoms
 - Medical history diagnoses
 - Emergency room visits, hospitalizations, and procedures since the last visit
 - Medication use since the last visit
 - Gastroparesis symptoms inventory including the global overall relief and the clinical global patient impression questions

When

- Visits f03, f06, f09, f12, f15 and f18

How

- Mix of interview data and data obtained by chart review
 - Questions on the FH form can be answered by interview with the patient – i.e., use all sources to get the most accurate information that you can
 - Attach a preprinted MACO label to page 5, Gastroparesis Symptoms Inventory, before separating and giving the questionnaire to the patient for completion
 - Clinical coordinator should check the returned page for missing items or other problems for resolution before the patient leaves the clinical center
 - Page 5 should be re-attached to the FH form.
-

6.8. Physical Examination (PE form)

Who

- All NORIG patients

When

- During screening and at follow-up visits f09, f12, and f15

What

- Height
- Weight
- Vital signs
 - Temperature
 - Blood pressure
 - Resting radial pulse
 - Respiratory rate
- System review
 - Chest and lungs
 - Heart
 - Abdomen, liver and spleen
 - Nervous system
- Anthropometry
 - Waist and hip circumference
- Electrocardiogram (ECG) is required during screening and at follow-up visits f09 and f12. Use Flash card #7 to guide your review of the electrocardiogram. If patient's QTc interval is greater than 450 milliseconds, the patient should be referred to cardiology for further evaluation for prolonged QT syndrome or other cardiac abnormalities. If ECG findings during screening are incompatible with NORIG participation, the participant is ineligible. If ECG findings are found during follow-up, they should be documented on the Interim Event (IE) form
- A negative pregnancy test for women of childbearing potential is required during screening to be eligible for randomization into the NORIG trial. If a pregnancy test is positive during follow-up, this should be documented on the Interim Event (IE) form

How

- Ideally, use a stadiometer for height measurement
 - Ideally, use the Gulick II tape measure for waist and hip measurement; this device may be obtained from www.fitnessmart.com (608-735-4718, model 67019, listed at \$36); it is manufactured by Country Technology Inc: 608-735-4718
 - See SOP sections 6.10 and 6.11 which detail the protocols for measurement of height, weight, waist circumference, and hip circumference
-

6.9. Height and weight measurements

Height measurements

- Height may be recorded in inches or centimeters
- Ideally, a wall-mounted stadiometer with a horizontal measuring block (or fixed angle) is used; other height measuring devices are acceptable
- Follow the manufacturer's recommendation regarding method and frequency of calibration of the stadiometer
- The patient stands erect on the platform with his/her back parallel to the vertical mounted measure scale (but not touching the wall), looking straight ahead with his/her head in the Frankfort horizontal plane (the horizontal plane defined by the lower margin of the bony orbit (the bony socket containing the eye) and the most forward point in the supratragal notch (the notch just above the anterior cartilaginous projections of the external ear))
- The horizontal measuring block is brought down snugly, but not tightly, on the top of the head
- Record the height to the nearest tenth of the unit of measurement (1 decimal place)

Weight measurements

- Follow the manufacturer's recommendation regarding method and frequency of calibration of the scale
 - Weight may be recorded in pounds or kilograms
 - Ideally, weight is measured in the morning after voiding and before breakfast; if this is not possible, try to measure the patient's weight at the same time of day and under the same conditions as the baseline measurements are obtained
 - Patient should be wearing light clothing (e.g., short sleeve shirt or blouse or surgical gown), shorts, socks and without shoes; pockets should be empty
 - Patient should stand still in the middle of the scale platform with head erect and eyes looking straight ahead
 - Record the weight to the nearest tenth of the unit of measurement (1 decimal place)
 - Patients who have limb amputations or who are wearing casts should have weight measured, but note this on the form on the margin (the notes may be keyed at data entry in the General Comments area of the keying)
-

6.10. Waist and hip circumference measurement

- Waist and hip circumference may be recorded in inches or centimeters
- Two measurements are recorded
- Ideally, a Gulick II Tape Measure will be used; this tape measure is designed to eliminate the guesswork by applying a known amount of tension (4 ounces) to the measuring tape; when used properly, tape tension is always 4 ounces; the self-retracting tape is kept at the desired length until the retract button is pushed
- If an ordinary tape measure (without the special 4 ounce tension indicator device) is used, the measurement will be affected by how tightly the tape is pulled
- Patient should be wearing light clothing (e.g., short sleeve shirt or blouse or surgical gown), shorts, socks and without shoes; pockets should be empty
- Ideally, waist and hip circumferences are measured in the morning after voiding and before breakfast; if this is not possible, try to measure the patient's waist and hips at the same time of day and under the same conditions as the baseline measurements are obtained

Waist circumference measurement

- Patient should stand with feet together
- Pull an appropriate amount of tape out of the housing
- Ask the patient to bare his/her waist
- Wrap the tape once around the waist: the measure should be taken around the abdomen horizontally at the midpoint between the highest point of the iliac crest and lowest part of the costal margin in the mid-axillary line
- Mark the midpoint on both sides of the patient using a washable marker
- Patient may be asked to assist in passing the tape around the abdomen by holding the end of the tape in position
- When the tape is positioned in the horizontal plane at the correct height, the patient should be asked to keep his/her arms at the sides and breathe naturally; ask the patient to breathe in and out and hold at the end of a normal exhalation
- Align the tape's zero line along side of the tape graduations; pull on the end of the tensioning mechanism until you see just one colored bead
- Record the measurement to the nearest tenth (one decimal place)
- Remove the tape, retract the tape, and repeat the procedure
- If the tape cannot be made horizontal across the waist markings, default to the right hip and note this in the margin of the form

Hip circumference measurement

- Ask the patient to adjust his/her clothing to allow measuring the hips over the patient's underwear

6.11. Waist and hip circumference

- Wrap the tape once around the hips over the underwear: the measure should be taken at fullest part of the hips (maximum extension of the buttocks)
 - Patient may be asked to assist in passing the tape around the hips by holding the end of the tape in position
 - When the tape is positioned correctly, the patient should be asked to keep his/her arms at the sides and breathe naturally; ask the patient to breathe in and out and hold at the end of a normal exhalation
 - Align the tape's zero line along side of the tape graduations; pull on the end of the tensioning mechanism until you see just one colored bead
 - Record the measurement to the nearest tenth (one decimal place)
 - Remove the tape and repeat the procedure
-

6.11. Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) (GD form)

What

- Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)

Purpose

- To obtain a NORIG trial participant's views of the severity of his/her gastroparesis symptoms

When

- Screening visit s1 or s2
- All follow-up visits (i.e., visits f03, f06, f09, f12, f15 and f18)

Procedure

- Clinical Coordinator should complete section A. Center, patient, and visit identification and apply preprinted MACO labels to pages 2-3 before giving the questionnaire to the patient to complete
 - Self administered
 - **Clinical Coordinator should check returned questionnaire for completeness and complete the scoring section B items 8-11 before the patient leaves the clinical center**
 - The total GCSI score is the sum of the 3 subscores in items 8, 9 and 10. The maximum total score is 45.
 - During screening the total GCSI score must be 21 or greater to be eligible for the NORIG trial; if the GCSI is less than 21, the patient is not eligible at this visit but may be re-screened at a later visit using a new GD form. Do not key the form to the data system in an Ineligibility is reached
-

6.12. Gastrointestinal symptoms rating scale (GSRS) (GS form)

What

- Gastrointestinal symptom rating scale (GSRS)

Purpose

- To collect data on the symptoms the patient has been experiencing during the NORIG trial.

When

- Screening visit s1 or s2
- All follow-up visits f03, f06, f09, f12, f15, and f18

How

- Clinical Coordinator should complete section A. Center, patient, and visit identification of page 1 and apply preprinted MACO labels to pages 2-7 before giving to the patient to complete the questionnaire
 - The Clinical Coordinator should review pages 2-7 for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be re-attached to pages 2-7.
-

6.13. Brief Pain Inventory (PI form)

What

- Brief Pain Inventory

Purpose

- To assess the severity and impact on daily functions of the patient's pain in the NORIG trial.

When

- Screening visit s1 or s2
- Follow-up visits f09 and f12

Procedure

- Clinical Coordinator should complete section A. Center, patient, and visit identification of page 1 and apply preprinted MACO labels to pages 2-4 before giving to the patient to complete the survey
 - The Clinical Coordinator should review pages 2-4 for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be re-attached to pages 2-4.
-

6.14. State-Trait Anxiety Inventory (Self-Evaluation Questionnaire) (SE form)

What

- Self-Evaluation Questionnaire (STAI)

Purpose

- To collect data on the psychosocial aspects of gastroparesis in NORIG participants

When

- Screening visit s1 or s2
- Follow-up visits f09 and f15

Procedure

- Clinical Coordinator should complete section A. Center, patient, and visit identification and apply preprinted MACO labels to pages 2-4 before giving to the patient to complete the questionnaire
 - The Clinical Coordinator should review pages 2-3 for missing responses and resolve any problems before the patient leaves the clinical center. Page 1 should be re-attached to pages 2-4 and the Clinical Coordinator should use the scoring key on page 4 to calculate the Y-1 and Y-2 scores to complete item 8 on page 1.
 - Only items 1-10 on page 1 are keyed into the NORIG data system.
-

6.15. Beck Depression Inventory (BD form)

What

- Beck Depression Inventory Questionnaire

Purpose

- To collect data on the psychosocial aspects of gastroparesis in NORIG participants

When

- Screening visit s1 or s2
- All follow-up visits (i.e., visits f03, f06, f09, f12, f15 and f18)

Procedure

- Clinical Coordinator should complete section A. Center, patient, and visit identification and apply preprinted MACO labels to pages 2-9 before giving the questionnaire to the patient to complete
- Self administered
- **Clinical Coordinator should check returned questionnaire for completeness and complete the scoring section items 8-11 before the patient leaves the clinical center,**
- The score is the sum of 21 items. If the patient has made more than one choice for an item, use the highest scoring item. The maximum total score is 63.

The box below provides guidelines on depression level for patients within certain scoring ranges.

Total Scores	Range
0-13	minimal
14-19	mild
20-28	moderate
29-63	severe

- Special attention should be paid to item 2 and to item 9. Patients admitting to suicide ideation (as measured by item 9) and/or hopelessness (as measured by item 2) with a rating of 2 or 3 should be flagged for further clinical care.
 - Special attention should be paid to item 16 (changes in sleeping pattern) and item 18 (changes in appetite). Where there are seven answer options (0, 1a, 1b, 2a, 2b, 3a, 3b). If a patient indicates a different answer for either of these questions as compared to when they last completed the form, this should be noted for clinical care.
 - Implement a plan of action per the NORIG protocol and your clinical center's guidelines for caring for patients with:
 - a total score between 29-63;
 - a response of 2 or 3 on item 2 or item 9.
-

6.16. SF-36 Health Survey (QF form)

What

- The SF-36 Health Survey is a 36-item patient reported survey (QF) form

Purpose

- To evaluate correlations between self-reported quality of life and disease severity in NORIG trial participants

When

- Screening visit s1 or s2
- Follow-up visits f09 and f15

Procedure

- Clinical Coordinator should complete section A. Center, patient, and visit identification and apply preprinted MACO labels to pages 2-7 before giving the questionnaire to the patient to complete
 - Self administered
 - Clinical Coordinator should review the returned questionnaire for missing responses and resolve any problems before the patient leaves the clinical center
-

6.17. Patient Health Questionnaire (PHQ-15) (PQ form)

What

- Patient health questionnaire is a 15-item patient reported measure

Purpose

- To obtain the patient's views of his/her health during the NORIG trial

When

- Screening visit s1 or s2
- Follow-up visits f09 and f15

Procedure

- Clinical Coordinator should complete section A. Center, patient, and visit identification and apply a preprinted MACO label to page 2 before giving the questionnaire to the patient to complete
 - Self administered
 - Clinical Coordinator should review the returned questionnaire for missing responses and resolve any problems before the patient leaves the clinical center
-

6.18. Laboratory Results (LR form)

Who

- All NORIG patients

What

- Form LR records laboratory results for tests done during screening and follow-up
 - Hematology
 - Hepatic panel
 - Metabolic panel, including magnesium
 - Thyroid stimulating hormone

When

- All laboratory results are required during screening
- Hematology, hepatic panel and metabolic panel including magnesium are required at f12
- When laboratory results are available during follow-up

Instructions for form LR

- The measures on form LR are intended to be obtained by chart review, both at screening and during follow-up
 - During screening, if the chart review tests are outside the 16 week time window or the test conditions can't be ascertained or differ from what is required, the chart review tests cannot be entered on the LR form and the tests should be repeated
 - During follow-up, the results must be within the time window for the follow-up visit
-

6.19. Plasma collection for Biosample Repository (BP form)

Purpose

- Collection of whole blood from NORIG patients for plasma banking
- Separation of plasma at clinical center: up to ten - fourteen 0.5 mL aliquots of plasma are to be aliquoted in 2.0 mL cryogenic vials
- Store plasma aliquots at -70° C prior to batch shipping to the NIDDK Biosample Repository at Fisher BioServices each month

Forms / Materials

- BP - Blood Processing for Plasma
- Preprinted MACO labels for heparin (green top) tube and BP form
- Choose one of the cryovial label sets provided by the DCC, ensuring the patient ID is correct
- Barcode scanner
- SS - Specimen Shipment log
- NIDDK Biosample Repository shipper

When

- Screening visit s1 or s2
- Follow-up visits f12, and f15
- Batch shipments: Monthly or more often as needed

By whom

- Phlebotomist
- Clinical Coordinator

Equipment

Blood tubes/aliquot vials

- One 10 mL sodium heparin (green top) tube - *provided by clinical centers*
 - Model/product number: Becton Dickinson product number #367874
 - 100 tubes/pack @ \$41.49
- 10-14 2.0 mL cryogenic vials - *provided by clinical centers*
 - vials should be able to withstand -196 degrees C
 - vials should be self standing (flat bottom, not curved), externally threaded, 13.5 mm wide x 48.3 mm tall, with silicone washers
 - Vendors contact information:
 - 1) Cryogenic Storage Systems and Supplies- Model #CV200-2
243 Lawyers Road, NW
Vienna, VA 22180
703-319-8247
877-738-8247
703-938-9351 (fax)

6.19. Plasma collection for Biosample Repository (BP form)

- 2) Corning External Thread Cryogenic Vials
Catalog # 430659
50 per pack, 500pk/case: \$204.17
Telephone: 1-800-492-1110
- 3) Fisher
1-800-766-7000
Catalog #10-500-26

Labels

- Preprinted MACO labels for whole blood collection tubes (10 mL heparin tube) and for Form BP – MACO labels are printed at the clinical center via web-based data management system; use MACO ML-5000 1" x 1 ½" labels, 50 labels/page
- Preprinted polypropylene labels for 2.0 mL cryogenic vials – provided by the DCC

Equipment

- Centrifuge
- -70° C freezer
- Swing out rotor
- 5 mL pipettes

Preparation for blood collection*Apply labels to cryovials*

- Attach the blue plasma polypropylene cryovial labels for aliquots #01-14 to the vials when the vials are at room temperature (Label for aliquot #00 goes on the BP form)
- Leave the cap on the vial when labeling; the inside of the vial is sterile
- Apply the label to the vial so that the long edge of the label is parallel to the floor when the vial is held in an upright position. The label should not trail off the bottom of the vial or over the cap
- While holding the vial in an upright position, affix the colored portion of the label to the vial first
- Wrap the clear tail around the perimeter of the vial. The end of the clear tail should overlap the colored portion of the label
- Press firmly on the entire label. Verify that all edges of the label adhere to the vial
- When possible, allow newly labeled cryovials to set at room temperature for several hours prior to subjecting them to colder temperatures. (24-48 hours is optimal)

Blood collection and processing procedures

- Blood for plasma to be centrifuged, aliquoted, and frozen within one hour
- If sample appears to have hemolyzed; do not aliquot. Re-draw blood.
- Patient instructed to fast 8 hours prior to blood draw
- Ensure that heparin tubes have not expired (*check that date shown above "Exp" in lower right corner of tube label is later than current month*).
- Collect whole blood into one heparin (green top; Becton-Dickinson #367874) tube.

6.19. Plasma collection for Biosample Repository (BP form)

- Affix the patient and visit specific MACO label to the heparin tube
- Completely fill vacutainer tube
- Mix gently by inversion 5 times
- Within 30 minutes, centrifuge at 1800 x g for 15 minutes at 4° C, preferably with a swing out rotor
- Immediately after centrifugation, insert a 5 mL pipette below surface of plasma
- Remove the clear plasma while avoiding blood cells
- Transfer plasma into aliquots of 0.5 mL each into up to 10-14 labeled 2.0 mL cryovials
- Freeze at -70° C immediately
- Discard the any remaining labeled cryovials with the same LS code
- Discard all red serum polypropylene cryovial labels with the matching LS code

Note: Plasma aliquots may be stored at -20° C for a few hours and a maximum of up to one day before transfer to -70° C . Make arrangements with your laboratory technicians as needed to ensure samples remain frozen during the transfer.

Blood Processing for Plasma (BP) form

- Complete the Blood Processing for Plasma (BP) form
- Affix duplicate MACO label for the heparin plasma tube to the BP form
- Affix the blue plasma cryovial label for aliquot #00 to the BP form

Packaging Procedures

- Check that 1 absorbent pad is in the Saf T Pack Bio hazard plastic bag
- Insert frozen cryovial into small cardboard boxes with dividers. Place only one tube into each cardboard cell. Each cardboard box may hold 81 cryovials
- Insert each cardboard box with cryovials into its own plastic bag and seal
- Place each plastic bag with specimen box into its own STP-710 Tyvek envelope and seal.
- Place each Tyvek envelope into STP-111 inner brown cardboard box. No more than 3 Tyvek envelopes containing boxes with cryovials can be placed into the STP-111 inner brown cardboard box. If shipping only 1 or 2 specimen boxes, fill the rest of the space inside the cardboard inner box with bubble wrap to prevent movement
- Tape the inner cardboard box closed before placing the styrofoam cooler
- Place cardboard box in upright position in bottom of styrofoam cooler
- Surround the STP-111 inner brown cardboard box with about 8 kg of 2" blocks or nuggets of Dry Ice
- Fill excessive room left in the insulated freezer box with bubble wrap to stabilize specimens in transit
- Place the polystyrene lid onto the freezer box
- Place the "Empty Packaging" cover and shipping form on the top of the cooler lid
- Place a completed Specimen Shipment Log with Excel spreadsheet attached on top of the cooler lid
- Close and seal outer cardboard box with tape

6.19. Plasma collection for Biosample Repository (BP form)
Labeling Shipper:

- Place a checkmark in the block on the outer cardboard box next to “BIOLOGICAL SUBSTANCE, CATEGORY B”. Do not cover this marking with labels.
- Affix a label with your name and return address to the side of the box in the “Shipper:” block
- Affix the repository address label to the side of the box in the “Consignee:” block
- Affix the dry ice label below the repository address label. Enter the weight of dry ice on the label in kilograms
- Affix the “UN3373 BIOLOGICAL SUBSTANCE, CATEGORY B” label to the right of the dry ice label
- Use the preprinted Federal Express air bill to ship specimens to the NIDDK Biosample Repository. Complete return address (leave “Sender Federal Express account number” blank). Section 6, Special Handling: Check “Yes, Shippers Declaration not required,” check “Dry Ice” block and entry “1” x “8”kg. Section 7, Enter “1” under “Total Packages” and the total weight of 24 lbs. Place completed Federal Express Airbill on side of box adjacent to the labeled side. Call Federal Express at 1-800-463-3339; give them the account number in section 7 of the Airbill

Do not write on exterior of box

Do not ship frozen packages on Friday; the repository is closed on weekends

Shipping samples to the NIDDK Biosample Repository

- Specimens are to be batch-shipped monthly to Fisher BioServices on Monday, Tuesday, or Wednesday
 - Aliquots will be stored locally at the clinical center at -70° C prior to shipping
 - Ship specimens in the STP 320 Saf T Pak shipper (provided by the NIDDK Biosample Repository); each shipper can accommodate aliquots for 16 patients, depending on the number of aliquots obtained for each patient (maximum capacity of each shipper is 230 aliquots)
 - Open the template Excel file used for shipments and scan each cryovial using the barcode scanner provided to your clinical center. The file should have the filename GpCRC_Site6xx_shipdate.xls. Replace the xx with the last 2 digits for your clinical center’s site ID and replace ship date with the date of shipment.
 - The Excel shipping file has column headings for barcode number, Site ID-Patient ID, Patient code, date collected, plasma; volume, units of measure, study number and visit code. You must complete all of these columns.
 - Complete section A. Center ID, shipment, and study information and section B. Clinic administrative information of the Specimen Shipment Log (SS) form. **Enclose a printed copy of the Specimen Shipment Log and the Excel spreadsheet with each shipment of specimens.**
 - Keep a notebook of all original completed Specimen Shipment Logs (Form SS) and spreadsheets so that you have a record of all shipments to the Biosample Repository
 - Email the Excel spreadsheet to the Biosample Repository at bio-niddkrepository@thermofisher.com with the Fed Ex tracking number in the subject line of the email.
-

6.20. Blood collection for Genetics Repository (BC, CG and GP forms)

Purpose

- Collection of blood from NORIG patients who consent for genetic research
- Shipment of blood to the NIDDK Genetics Repository at Rutgers University for DNA banking

Forms

- NORIG consent for genetic research
- Genetic Consent Documentation (CG) form
- Blood Collection for DNA (BC) form
- NIDDK Genetics Initiative Phlebotomy (GP) form

When

- Screening visit s1 or s2 or any time during follow-up if unable to obtain during screening or due to a low yield of DNA from initial collection (less than 100 micrograms of DNA), for participants who have not previously consented to DNA banking
- Ship same day as blood collection; **Monday - Friday**

By whom

- Clinical Coordinator and Study Physician (to obtain consent)
- Phlebotomist (to obtain whole blood)
- Person responsible for shipping whole blood to NIDDK Genetics Repository

Equipment

- Two 10 mL NaEDTA vacutainer tubes (purple top) - *provided by NIDDK Genetics Repository*
- Preprinted MACO whole blood tube labels and form BC labels - *provided by clinical centers (printed from web based data management system; clinical center provides MACO ML-5000 labels (1" x 1 ½ ", 50 labels per page, www.acco.com/wilsonjones/productdetails.aspx?s=08pid=mml-010)*
- Shipper - *provided by NIDDK Genetics Repository*
 - One model 470 Thermosafe Safety Mailer (styrofoam body and lid)
 - One 2 ½" x 9" pre-cut section of absorbent materials
 - Two 18" strips of red waterproof tape
 - One press-lock plastic bag
 - One corrugated shipping carton with locking tabs
 - One assembly instructions for Model 472 Thermosafe Safety Mailer

6.20. Blood collection for Genetics Repository
Blood collection procedures

- Collect blood into two 10 mL NaEDTA (purple top) tubes
- Invert each tube gently 6 times to mix blood with additives
- Keep blood at room temperature
- Check that patient ID information on preprinted MACO tube labels matches information recorded onto the NIDDK Genetics Initiative Phlebotomy form
- Phlebotomist should sign and date the section: To Be Completed by Phlebotomist on the NIDDK Genetics Initiative Phlebotomy form

Applying labels to tubes

- Apply the MACO labels over the paper vacutainer labels already on the tubes.
- Leave the cap on the tube when labeling; the inside of the tube is sterile

Packaging procedures

- Ship whole blood at ambient room temperature same day to the NIDDK Genetics Repository
- Package the whole blood tubes in the body of the Safety Mailer (Model 472 Thermosafe Safety Mailer)
- Tear off one section of absorbent materials along perforates and place it so it exactly covers cavity of the Safety Mailer
- Place lid of Safety Mailer over body and absorbent material and press down firmly so that lid closes properly. Reposition absorbent material so that it does not get caught between the lid and body
- Peel backing from two 18" long pieces of red waterproof tape and seal the Safety Mailer lid to the body; peel backing from second piece of tape and continue sealing the mailer, overlapping the first piece of tape about two inches on both ends
- Place the sealed Safety Mailer into the press-lock plastic bag. **Do not seal the bag.**
- Place the NIDDK Genetics Initiative Phlebotomy form in the mailer box outside the plastic bag
- Slide the Safety Mailer and open press-lock bag into the corrugated carton
- Seal the press-lock bag and close carton using the locking tabs
- Place sealing tape (not included) over them

Shipping procedures

- Use the preprinted Federal Express shipping label, marked for *Priority Overnight Delivery*, to ship whole blood to the NIDDK Genetics Repository, Monday - Friday
- Affix the "UN3373 BIOLOGICAL SUBSTANCE, CATEGORY "B" label to the outside cardboard box
- Call Federal Express, 1-800-Go-FEDEX (1-800-463-3339) for courier. *Due to inconsistent Federal Express delivery around holidays and likelihood of closure of the Genetics Repository on holidays, do not schedule deliveries on the day before or the day of a*

6.20. Blood collection for Genetics Repository

national holiday. Check with Federal Express and with the Genetics Repository if there is any question about delivery availability or closure.

- Notify Dana Witt at the NIDDK Genetics Repository that blood is being shipped and provide the Federal Express tracking numbers and the NIDDK ID numbers. Notification may be via:
 - Web Portal: <http://rucdr.rutgers.edu/shippingblood>
(additional information regarding this portal is at the end of this section)
 - Fax: 1-732-445-1149
 - Telephone: 1-732-445-1498
- Ship whole blood to:
 - Rutgers University/Cell Repository/NIDDK
 - 604 Allison Rd., Room C120A
 - Nelson Laboratory
 - Piscataway, New Jersey 08854-8000

Genetics Repository Web Portal System

(Rutgers University Cell and DNA Repository - RUCDR)

- Establishing a Username and Password
https://rucdr.rutgers.edu/scripts/up.exe?AIMACTION=vnewaccountconiddk&enforce_color=ON&skey=10925637151082500795
- Click on the URL listed above and then just follow the directions on the top of the page. You can sign up for multiple NIDDK sites (if you are associated with more than one) at once. (Phlebotomists performing off-site draws will send a notice from <http://rucdr.rutgers.edu/shippingblood>)

Logging in to the System

- The URL for the RUCDR Web Portal is <http://rucdr.rutgers.edu>. Click on the square for NIDDK to get to your login screen. Enter your newly created username and password. If you ever forget your username or password there is an option on this screen to "Retrieve Lost Password". You will need to remember what email address you used to create your account to use this function!

Announcement Board

- When you enter the web portal you will see announcements from the RUCDR. The dates of future holiday closings will be listed here.

Navigating the Web Portal

- Click the tabs on the top of the screen to access the different parts of the web portal. The functions accessible from each tab are listed below.

6.20. Blood collection for Genetics Repository

Ordering additional shipper kits

- Additional blood collection kits can be requested through the web portal. The repository will supply the kits in sets of 25 but please make sure they are ordered at least three weeks in advance. They take time to assemble and ship.

Request Functions

- From the "Request Functions" tab you can do two things: "Submit Request" or "Look Up Status of Request".

1. Submit Request

- To get to these options, pick a function from the drop-down menu: Shipping Blood, Request Mailers, or Question.
- Next, pick a site number from the drop-down menu.
- Fill out the section of the form corresponding with the function you chose. Even if your function choice was not "Question" you can add information to any request in the textbox under the heading "Special Notes/Special Instructions/Questions".
- *Good thing to know! If you choose "Shipping Bloods" you can only enter one FedEx tracking number per submission, but if you have more than one sample in the box you can list all the NIDDK ID numbers separated by commas. As always, do not overpack the mailers and enclose a separate piece of paperwork for each sample.*
- In Section 2: Attachments (a light grey area towards the bottom of the page) you can add a file.

2. Look Up Status of Request

- You can search your recent requests to see their status in multiple ways. These are self-explanatory. If you just hit the search button without selecting any search criteria all the requests you have made will be shown.
- There are 4 different status assignments a request can have:
 - Open
 - Assigned
 - Pending
 - Closed
- **Open:** This status signifies that a request has been submitted, but is not yet assigned.
- **Assigned:** This status signifies that an open request is assigned to a particular staff person.
- **Pending:** This status signifies that a request has been assigned and a staff person is working on it, but hasn't yet completed the job.
- **Closed:** When a request is completed the status is set to closed.

6.20. Blood collection for Genetics Repository**Self Help Resources**

- This tab is a holding area for useful documents.
 1. **FAQ** – If you have a question, hopefully it is already answered here.
 2. **Download Center** – These instructions are here! Also, any paperwork enclosed with mailer kits is here in case you need to print off extras.
 3. **View Announcements** – In case you missed the announcement page when you first logged in to the web portal you can read it again.
 4. **Support Resources** – Links that may be of interest to visit.

Account Management

- From this tab you can "Modify Your Profile" or "Change Password".

Important Information Regarding Blood Shipments

- When a package is received, a mailer request is filled or a question is answered, you will receive an email from us and the status will be changed to "closed".
-

6.21. Drug Dosing Determination and Dispensing (DD form)

Purpose

- To document the dosage the patient is currently taking and the new dosage prescribed at each visit

When

- Randomization visit (Rz)
- Follow-up visits f03, f06, f09, f12, and f15 visits

Dispensing of study drug

- Study drug is to be dispensed to patient at: randomization, weeks 3, 6, 9, 12 and as needed for tapering at week 15
- At each visit, the patient should return all bottles of study drug to the coordinator (even those unopened or unused). The DD form should be completed and new drugs should be issued according to the dosage indicated on the DD form. Once the DD form is keyed to the data system, the RD form should be completed to document the capsules and bottle numbers returned as well as the bottle numbers dispensed at each visit.
- Do not attempt to “re-use” bottles of study drug already dispensed to the patient, always collect all study drug bottles at each visit, and dispense new study drug bottles.

By whom

- Clinical coordinator or pharmacist

Procedures at clinical center

- The DD form must be keyed after the patient is randomized into the NORIG trial to receive the bottle number to be dispensed to the patient
- The DD form must be keyed at every follow-up visit to receive the bottle number(s) to be dispensed to a patient at that visit

Dose escalation schedule

<i>Visit</i>	<i>Scheduled Dose</i>	<i># bottles</i>	<i>Comment</i>
rz	10 mg	1	3 week supply (10 mg capsule each day)
f03	25 mg	1	3 week supply (25 mg capsule each day)
f06	50 mg	2	3 week supply (25 mg capsules each day)
f09	75 mg	3	3 week supply (25 mg capsules each day)
f12	75mg	3	3 week supply (25 mg capsules each day)
f15		--	As needed for tapering

6.22. Drug Dosing Determination and Dispensing (DD)**Tapering schedule**

- If patient's dose at f15 visit is 75 mg (*three 25 mg capsules each day*): patient should be tapered to the 50 mg dose (*two 25 mg capsules each day*) for one week, then tapered to the 25 mg dose (*one 25 mg capsule each day*) for one week and no study drug for last week
 - If patient's dose at f15 visit is 50 mg (*two 25 mg capsules each day*): patient should be tapered to the 25 mg dose (*one 25 mg capsule each day*) for one week
 - If patient's dose at f15 visit is 25 mg (*one 25 mg capsule each day*): patient should be tapered to the 10 mg dose (*one 10 mg capsule each day*) for one week
 - If patient's dose at f15 visit is 10 mg (*one 10 mg capsule each day*): no tapering is required, the patient should stop taking the study drug, do not dispense study drug at this visit.
-

6.22. Study drug dispensing and return (RD form)

Purpose

- To document dispensing and return of study drug and accounting for unused capsules and empty study drug bottles

When

- Study Drug Dispensing and Return (RD) form should be completed and keyed at the Rz, f03, f06, f09, f12, f15 and f18 visits

Dispensing of study drug

- At each visit, the patient should return all bottles of study drug to the coordinator (even those unopened or unused). The DD form should be completed and new drugs should be issued according to the dosage indicated on the DD form. Once the DD form is keyed to the data system, the RD form should be completed to document the capsules and bottle numbers returned as well as the bottle numbers dispensed at each visit.
- Study drug is to be dispensed to patient at: randomization, weeks 3, 6, 9, 12 and as needed for tapering at week 15

Drug supply

- Nortriptyline and placebo nortriptyline: 10 mg capsule or 25 mg capsule; 30 capsules per bottle, to be taken orally once a day (qd) 30 minutes before bedtime.

Checks on return of study drug

- Unused study drug to be returned by patient at: Weeks 3, 6, 9, 12, 15, and 18

By whom

- Clinical coordinator or pharmacist

Procedures at clinical center

- Maintain study drug inventory of current drug supplies
- Maintain log of study drugs returned, destroyed or disposed
- Study drug supplies are shipped to arrive within 2 working days of order
- Notify the DCC if your supplies are low or if you do not receive an expected shipment

Handling and disposal

- Unused portions of open bottles in the possession of patients should be considered contaminated and handled accordingly
- Returned capsules should be counted by the pharmacist or clinic coordinator and the number of capsules and the number of bottles returned, should be recorded on the RD form
- All unused capsules returned by patients should be disposed per the drug disposal policy of your institution

6.23. Study drug dispensing and return (RD)**Storage and stability**

- Store in a cool dry place at 77° F (25° C), excursions permitted to 59° F to 86° F (5° C to 30° C).
 - Keep container tightly closed
-

6.23. Standardized management of side effects

Purpose

- To ensure all NORIG patients receive the same management of their common side effects and to provide guidance for the management of more serious side effects.

A standardized management plan for the most common side effects as well as the more serious side effects are outlined below:

COMMON SIDE EFFECTS

Side effect severity	Investigator response
Noticeable but tolerable	Continue therapy and dose escalation
Bothersome and barely tolerable	Reduce dosage to the last dose tolerated without stopping treatment
Intolerable	Discontinue nortriptyline for one week and then restart it at the lower dosage that was previously tolerated

Endocrine metabolic:

Weight gain - Continue study medication with dose escalation as planned.

Gastrointestinal:

Constipation - Continue study medication with dose escalation as planned. Recommend patient to add fiber supplement and to increase fluid intake and drink eight ounce glasses of water daily.

Loss of appetite - Continue study medication with dose escalation as planned.

Nausea - Continue study medication with dose escalation as planned.

Bloating - Continue study medication with dose escalation as planned.

Dry Mouth - Continue study medication with dose escalation as planned. Patient can use sugarless hard candy, gum, or ice chips. Saliva substitutes may be needed.

Neurologic:

Asthenia - Continue study medication with dose escalation as planned.

Dizziness - Make sure patient is taking entire dose at bedtime. This symptom generally subsides after a few weeks. If continues, reduce dose to prior tolerable dose and maintain this dose for

6.23. Standardized management of side effects

remainder of study. Usually dizziness is due to orthostatic hypotension and can be reduced by having the patient change positions slowly.

Headache - Continue study medication with dose escalation as planned.

Somnolence or drowsiness - Continue study medication with dose escalation as planned. Inform patient that this symptom generally subsides after a few weeks. Patient can move the time for medication from 30 minutes before bedtime to 60 minutes before bedtime. If continues, reduce dose to prior tolerable dose and maintain this dose for remainder of study.

Tremor - This symptom generally subsides after a few weeks. If continues and intolerable for the patient, reduce dose to prior tolerable dose and maintain this dose for remainder of study.

Confusion - Stop medicine for one week, and then restart at lower tolerable dose.

Cardiac:

Palpitations/Tachycardia: Obtain ECG and check QTc interval. If normal, stop medication for one week and resume at lower tolerable dose. If ECG is abnormal, instruct patient to stop taking the study drug, monitor and refer as appropriate.

Ophthalmic:

Blurred vision - Continue study medication with dose escalation as planned. This symptom generally subsides after a few weeks. If continues and intolerable, reduce dose to prior tolerable dose and maintain this dose for remainder of study.

Urinary:

Urinary Retention - Continue study medication with dose escalation as planned. This symptom generally subsides after a few weeks. If continues and intolerable, reduce dose to prior tolerable dose and maintain this dose for remainder of study.

Dermatologic:

Skin rash - Investigate if there are other potential causes for skin rash. If tolerable by patient, continue medication with dose escalation as planned. If skin rash worsens during the study, reduce dose to prior tolerable dose and maintain this dose for remainder of study. If skin rash continues to worsen, stop the study medication. Patient remains in study on no treatment.

Other:

Fatigue - Continue study medication with dose escalation as planned. Inform patient that this symptom generally subsides after a few weeks. Patient can move the time for medication from 30 min before bedtime to 60 minutes before bedtime. If continues, reduce dose to prior tolerable dose and maintain this dose for remainder of study.

SERIOUS SIDE EFFECTS FOR WHICH STUDY MEDICATION WILL BE STOPPED AND THE PATIENT WILL BE FOLLOWED ON NO TREATMENT.

6.23. Standardized management of side effects

Patients will call in if they develop blurred vision, rapid heart beat, chest pain, orthostatic hypotension, dizziness upon standing or difficulty urinating.

Cardiovascular:

Cardiac dysrhythmias, QTc prolongation (concern is for >440 – 450 msec in men or > 460 – 470 msec in women), concern for development of Torsades de Pointes or sudden death heartblock on ECG myocardial infarction (rare). Stop study medication. Ensure immediate follow-up with a cardiologist. Patient remains in study on no treatment. Repeat ECG after stopping study medication.

Hematologic:

Agranulocytosis (rare), bone marrow depression (rare), drug-induced eosinophilia (rare), thrombocytopenia (rare). Stop study medication. Ensure immediate follow-up with a hematologist. Patient remains in study on no treatment.

Hepatic:

Decreased liver function (rare), jaundice (rare). Stop study medication. Ensure immediate follow-up with a hepatologist. Patient remains in study on no treatment.

Dermatologic:

Signs of an allergic reaction – unexplained hives, unexplained swelling, wheezing, swelling of face, lips, tongue, or throat. Stop medicine. Instruct patient to call 911 or go to emergency room for immediate care. Patient remains in study on no treatment.

Neurologic:

Cerebrovascular accident (rare), seizure (rare). Stop study medication. Ensure immediate follow-up with a neurologist. Patient remains in study on no treatment.

Psychiatric:

Depression, worsening, suicidal thoughts, suicide - Stop medicine. Refer to mental health professionals. Patient remains in study on no treatment. Symptoms of aggressiveness, akathisia (psychomotor restlessness), agitation, anxiety, insomnia, irritability, hostility, mania, impulsivity, and panic attacks may represent precursors to emerging suicidality.

Treatment with antidepressant agents have been reported to paradoxically be associated with suicide in patients with primary depression. Primary depression is an exclusion for participation in the NORIG trial. We will monitor patients for the most common severe serious side effects (cardiac and psychiatric) by using standardized questionnaires for side effects and the Beck Depression Inventory (BDI) score. The Suicidal Thoughts or Wishes item in statement 9 on the BDI-II will be used to determine if a patient is suicidal. A score of 1 on this item (I have thoughts of killing myself, but would not carry them out) should initiate a referral to a mental health professional for further investigation. A score of 2 (I would like to kill myself) or 3 (I would kill myself if I had the chance) should result in contacting the mental health consultant (pager/phone) for discussion about

6.23. Standardized management of side effects

disposition, i.e., immediate meeting with the mental health consultant or getting the patient to the ER for possible inpatient treatment.

Also, severe depression is suggested by a patient response of 2 or 3 in the BDI-II statement 2 on Pessimism or a score of 28 or more total points on the BDI. With either a response of 2 or 3 on statement 2 or a total score of 28 or more, and in the absence of the suicide item trigger, this would result in a referral to the mental health consultant. Study staff will calculate the BDI total score and check statements 2 and 9 before the patient leaves. For each clinical center, a mental health professional (psychiatrist or psychologist) will be part of the study. Each consent form given to participants will have a self-referral list for psychological assistance if needed. In sum,

- If Severe Depression (BDI-II total > 28) with Statement 9 = 1; then refer for further mental health evaluation as soon as can be arranged (usually same day if patient is agreeable)
 - If Suicidal Ideation without intent on Statement 9 = 1; then refer for further mental health evaluation as soon as can be arranged (usually same day if patient is agreeable)
 - If Suicidal Ideation with possible intent on Statement 9 > 1; then contact mental health consultant immediately for further evaluation and disposition; handle as possible psychiatric emergency
-

6.24. Adverse event reporting (IE or SR forms)

Definitions

- **Adverse event (AE)** is defined as any unfavorable sign, symptom, state, condition, or laboratory finding in a NORIG patient. Adverse events may result from appropriate application of the protocol in relation to the processes of screening, or follow-up of NORIG participants, as well as from mistake or misadventure. An adverse event is any untoward medical occurrence that may present itself during treatment with a study drug or clinical procedure and which may or may not have a causal relationship with the treatment. Adverse events include any unanticipated problems involving risks to participants, or breaches of protocol which might entail risk to participants. The term "unanticipated problem" includes both new risks and increased rates of anticipated problems.
- **Serious adverse event (SAE)** is defined as any event that suggests a significant hazard, contraindication, or side effect. Serious adverse event includes any event that is fatal or life-threatening, is permanently disabling, requires or prolongs inpatient hospitalization, or is a congenital anomaly, cancer, or overdose. Other events may also be considered a serious adverse event if, based on medical judgement, the event jeopardized the patient to the point of requiring medical or surgical intervention to prevent the occurrence of any of the conditions for a serious adverse event listed above.
- **Unexpected adverse event** is defined as any adverse event that is not identified in nature, severity, or frequency in the risk information included in the NORIG trial protocol or current study drug package insert.
- **Associated with study drug** means that there is a reasonable possibility that the adverse experience may have been caused by the study drugs.

Reportable NORIG events

- Any serious and unexpected adverse event that may reasonably be regarded as caused by, or probably caused by, the study drug. If the adverse event is alarming, the investigator shall report the adverse effect immediately to all clinical centers, the Data Coordinating Center, the NIDDK project scientist, the Steering Committee, DSMB and the FDA.
- Any event threatening the integrity or well-being of the NORIG trial (e.g., suspected fraud) is a reportable event. We recognize that this category is not well-defined; however, it is included as a reminder that reportable events can have a broader scope than adverse events that happen to a patient.
- Deciding whether an event is reportable in the NORIG trial (i.e., is in either of these categories) will be the responsibility of the study physician of the clinical center. The study chair, the NIDDK project scientist, and staff at the Data Coordinating Center are available for consultation.
- Recent Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs — Improving Human Subject Protection from the FDA can be found here: <http://www.fda.gov/cder/guidance/OC2008150fnl.htm> or on the GpCRC website www.gpcrc.us – click on *Documents*.

6.24. Adverse event reporting (IE or SR forms)
CTCAE v3.0

- Events are reported on the either the Interim Event (IE) or IND Safety Report (SR) form
- The GpCRC uses the Common Terminology Criteria for Adverse Events, (CTCAE v3.0) to categorize and grade adverse events.
- This document is posted on the GpCRC website (www.gpcrc.us – click on *Documents*)
- Use the CTCAE v3.0 to specify the Short Name for the adverse event and the severity grade for the adverse event.

Clinical center responsibilities regarding reportable NORIG events that occur at your clinical center

- Your institution's IRB has reporting requirements of its own regarding events occurring in the course of conduct of a trial. These reporting requirements may be more stringent than those adopted by the NORIG trial. Regardless of what the NORIG trial requires, you must continue to meet your local IRB's requirements. If the local requirements are more stringent than the NORIG's, you may report events locally that you do not report to NORIG.
- If such an event occurs, appropriate medical care should be provided immediately in the clinic.
- If a suspected adverse event is reported by telephone several days later, the participant should be evaluated in the clinic by medical staff (preferable) or referred to an appropriate facility for evaluation and management.
- All such events should be documented in the study chart.
- You must notify the Data Coordinating Center about occurrence of events judged reportable to the NORIG trial as follows: If an event has occurred that you judge is reportable to NORIG, complete the Interim Event (IE) form. Key this form to the NORIG data system. Also send it to the Data Coordinating Center with a narrative description of the event and your subsequent course of action -- describe what happened, the actions taken in response to the event, and the relationship of the event to the NORIG study drug or procedures. Please refer to the patient by his/her GpCRC patient ID number and code; do not use the patient's name or other identifiers.

Serious Adverse Event reporting (IE or SR)

- Centers should use the Interim Event (IE) form to document adverse events and serious adverse events that in the opinion of the investigator are 1) expected, or thought to be associated with study drug but do not meet the criteria for Serious Adverse Event/IND Safety Report (SR) form or 2) not thought to be associated with the NORIG study drug
- Centers must use the IND Safety Report (SR) form to report serious adverse events that satisfy the IND Safety Report requirements outlined in the NORIG trial protocol, including the occurrence of a **serious** (fatal or life-threatening, results in significant or persistent disability, results in a congenital anomaly or birth defect, requires or prolongs hospitalization, or represents other significant hazard or serious harm to research subjects or others) **and unexpected** (not included in the NORIG protocol or in the package insert of nortriptyline) adverse event that, in the opinion of the investigators, is thought to be associated with NORIG study drug.

6.24. Adverse event reporting (IE or SR forms)

- If the serious adverse event is judged by the study physician to be associated with the study drug and unexpected per the package insert and above definitions, the SR form, together with a memo summarizing the circumstances of the event and the current status of the patient, must be faxed to the DCC and to the NIDDK project scientist within one working day of the discovery of the SAE and confirm receipt via email or telephone.
- The NIDDK project scientist will work with the DCC to transmit the IND Safety Report (SR) form and memo to the DSMB Chairperson and Steering Committee members, all participating center investigators and the FDA no later than 15 days from the discovery of the SAE (no later than 7 days if the SAE is fatal or life threatening).
- The DSMB Chair and NIDDK project scientist will determine if all DSMB members should be made aware of the event at that time, or it is appropriate to wait until the next DSMB meeting.
- The clinical center investigator may also complete an FDA MedWatch 3500 form.
- The DSMB will review each SAE report and provide comments to the NIDDK project scientist within one week of receipt of the report. If requested by any member of the DSMB, a teleconference will be scheduled to discuss the SAE and recommend any actions to the NIDDK sponsor.
- The clinical center must submit to the NIDDK project scientist and to the DCC a follow-up memo within one month of the SAE (and periodic updates if needed) to report the details of the disposition of the SAE.
- The NIDDK project scientist will work with the DCC to distribute the follow-up memo to the Steering Committee, all participating center investigators and to the DSMB.
- The DCC will maintain a list of such events for reporting and review at Steering Committee meetings and DSMB meetings.

How to Determine If an Adverse Event (AE) is an Unanticipated Problem that Needs to Be Reported

- Because they have been previously observed with a drug, the AEs listed in the investigator's brochure would, by definition, not be considered unexpected and thus would not be unanticipated problems. Possible exceptions would include situations in which the specificity or severity of the event is not consistent with the description in the investigator's brochure, or it can be determined that the observed rate of occurrence for a serious, expected AE in the clinical trial represents a clinically important increase in the expected rate of occurrence.
- There should be careful consideration of whether an AE is an unanticipated problem that must be reported to IRBs. The FDA believes that only the following AEs should be considered as unanticipated problems that must be reported to the IRB:
 - A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
 - A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).

6.24. Adverse event reporting (IE or SR forms)

- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). We recommend that a summary and analyses supporting the determination accompany the report.
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects.
- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence

Reporting deaths occurring in NORIG trial participants

- As soon as a clinical center is aware of a NORIG participant's death, the Study Physician and Clinical Coordinator should complete the Death Report (DR) form and send the DCC Center (Attn: Mika Green) the following; (1) A narrative description of the event including hospitalization information as applicable; (2) A copy of your report to your (IRB), as applicable.
 - The Death Report (DR) form should be keyed to the NORIG data system.
-

6.25. Procedures for missed or incomplete visits (MV form)

Purpose

- Record data about missed or incomplete visits in the NORIG trial

Form

- Missed or Incomplete Visit (MV) form

When

- The MV form should be completed within 7 days of the close of a visit window for any missed follow-up visit or for any follow-up visit with specific study procedures or data collection forms not completed

By whom

- Clinical Coordinator

Procedures for missed or incomplete in-person visits

- For a missed visit:
 - Date of missed visit is the last date of the visit window
 - Indicate reason(s) for missed visit
 - For an incomplete visit:
 - Date of incomplete visit is the date on which a partial set of procedures was performed
 - Indicate reason(s) for missed procedures
-

6.26. Procedures for patients lost to follow-up

Purpose

- Ascertain vital status of patient
- Document reason(s) patient did not attend visit
- Ascertain if patient is lost to follow-up

When

- Whenever patient misses a study visit and is difficult to contact

By whom

- Clinical coordinator

Search strategies

- Contact all persons identified on the Patient Location (PL) form
 - Telephone different times during the day/evening
 - Send letter via regular or certified registered mail to determine if patient is still at listed address
 - Check current telephone directory for listings both for the patient and the patient's contacts specified on the PL form, eg., next of kin, health care professionals
 - Check post office for forwarding address; ask patient's contacts for forwarding address
 - Check obituaries
 - Check state vital records
-

6.27. Procedures for mortality closeout (DR form)

Purpose

- Record a NORIG participant's death

Forms

- Complete the Death Report (DR) form
- Study Physician should attempt to access the medical records of the participant and submit a narrative on the nature of the death including co-morbidities leading to death, hospitalizations and other pertinent clinical information to the DCC and their local IRB as applicable.

By whom

- Study Physician and Clinical Coordinator
-

6.28. Transferring patients from NORIG to the Gastroparesis Registry (CO form)

Purpose

- To close out a patient's participation in NORIG and document the patient's consent to join or re-enter the Gastroparesis Registry (GpR)

Form

- Closeout (CO) form

When

- The NORIG Closeout (CO) form should be completed at the NORIG f18 visit (or at the close of the f18 visit window) for all patients randomized in the NORIG trial.

By whom:

- Clinical coordinator

Instructions

- Ask the patient if he/she consents to re-entering or enrolling in the Gastroparesis Registry
- Patients willing to join the GpR should sign the most recent version of the Gastroparesis Registry informed consent approved by your IRB (follow your institutional IRB guidelines for re-consenting participants previously enrolled in the GpR).
- Each consenting patient should be scheduled for a GpR follow-up visit approximately 14 weeks after the date of their NORIG f18 visit. For patients previously enrolled in the GpR, consult the patient's GpR visit schedule (time windows guide) generated at their enrollment and schedule the GpR follow-up visit that is open 14 weeks from the date of their NORIG f18 visit. GpR data collection will not resume until 14 weeks after the NORIG f18 visit. .
- For patients who were not previously enrolled in the Gastroparesis Registry, a new visit schedule (time windows guide) will be automatically generated when the NORIG Closeout form (CO) is keyed into the web-based data management system. The new visit schedule will use the NORIG randomization date as the effective date of enrollment into the GpR. Schedule the participant approximately 14 weeks from their NORIG f18 visit for their f032 GpR follow-up visit. GpR data collection will not begin until 14 weeks after the NORIG f18 visit. Certain laboratory values were not requested in the NORIG trial but are part of the screening process for traditional enrollment into the GpR. These values would be useful to capture in NORIG participants electing to participate in GpR. If available or when clinically indicated, please obtain and record on the GpR Laboratory Results (LR)

6.28. Transferring patients from NORIG to Gastroparesis

form, the lab values for anti-nuclear antibody (ANA), scleroderma antibody (Scl-70), C-reactive protein (CRP), serum electrophoresis (SPEP), prothrombin time (PT), International Normalized Ratio (INR), partial thromboplastin time (PTT), and hemoglobin A1c (HbA1c). You do not need to complete the GpR Genetic Consent Documentation (CG) or the GpR Blood Collection for DNA (BC) forms for participants that had blood drawn for DNA banking while in the NORIG trial.

- For NORIG participants who decline to participate in the Gastroparesis Registry; inform them that the study results and their treatment assignment will be available to them sometime after the close of the NORIG trial.
-

NORIG SOP Part I: Clinical Center Operations

7. Forms management

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7.1. Clinical center ID codes

Alphabetic IDs

- Alphabetic clinic IDs are used on forms, lists, and tables
- Alphabetic clinical center IDs are based on the name of the institution with which the clinical center is affiliated
- Assigned IDs

Stanford University	SU
– California Pacific Medical Center	CPMC
Temple University	TU
Texas Tech University Health Science Center	TTU
University of Michigan	UMI
University of Mississippi	UMS
University of Wake Forest	WFU

Numeric site IDs

- The NIDDK Genetics and Biosample Repositories use numeric IDs to identify the GpCRC clinical centers
- These will be used on the specimens (whole blood and plasma samples sent to the Genetic and Biosample Repositories, respectively)
- Assigned IDs

Stanford University	613
– California Pacific Medical Center	613
Temple University	610
Texas Tech University Health Science Center	637
University of Michigan	611
University of Mississippi	612
Wake Forest University Health Sciences	614
Johns Hopkins University- DCC	61

7.2. Patient identifiers

What

- Patient ID number
- Patient code

Patient ID number

- 4 characters, all numeric
- ID number labels will be distributed to clinics by the Data Coordinating Center
- The ID number for a patient will remain the same for the duration of the GpCRC, even if the patient enters another GpCRC study or if the patient fails screening and is subsequently re-evaluated – the ID never changes

Ranges of patient IDs assigned to clinics

Stanford University	SU	4001	-	4999
Temple University	TU	1001	-	1999
Texas Tech University Health Science Center	TTU	6001	-	6999
University of Michigan	UMI	2001	-	2999
University of Mississippi	UMS	3001	-	3999
Wake Forest University Health Sciences	WFU	5001	-	5999

Patient code

- 3 character alpha code assigned by the Data Coordinating Center and printed on the ID number label
 - Each patient code is unique across the GpCRC
-

7.3. Visit ID code

- 1 to 3 character alpha-numeric code
- Determined by purpose of visit and timing with respect to visit windows
- Visit ID codes

s1, s2	Screening, baseline data collection
rz	randomization
f03	3 weeks follow-up visit
f06	6 weeks follow-up visit
f09	9 weeks follow-up visit
f12	12 weeks follow-up visit
f15	15 weeks follow-up visit
f18	18 weeks follow-up visit
n	Unscheduled follow-up visit

7.4. General guidelines for forms completion

Ink

- Forms should be completed in ink that is dark enough to photocopy legibly; do not use pencil or colors (e.g., red, green, light blue, or purple) that do not photocopy well

Changing responses on forms

- If an error is made on the form, correct the response by marking through the response with one or two lines and writing the correct response next to or above the original response. The staff member making the correction should put their initials and the date in the margin by the correction. A brief explanation for the change should also be written in the margin; e.g., 'error', 'pt changed mind', 'wrong response checked'.
- Do not obliterate, erase, or white-out incorrect responses
- The idea is to preserve an audit trail of the original response and subsequent changes to it

Multipage forms

- The patient ID number should be written on the top right of every page of every form in the space provided -- protect yourself against ineffective staples and photocopying mishaps

Miscellaneous

- All written responses should be printed legibly so the responses can be keyed to the database
- Do not use abbreviations or short-hand that may not be easily understood or keyed in the written responses
- Numeric data should be recorded in the units prescribed on the form and to the level of precision (number of digits) indicated on the form
- All numbers should be right justified and leading and trailing zeroes should be recorded on the form where applicable (e.g., an age of 8 would be written and keyed as "08").
- All letter codes should be left justified with the remaining spaces left blank (e.g., a visit ID for the screening visit 1 would be completed and keyed as "s1").
- The clinical coordinator should review all responses for completeness and accuracy before signing off on the form
- Wherever possible, forms should be completed in real time, not retroactively. Interviews and questionnaires should be completed on the actual data form.
- The data on some forms, such as the Laboratory Results (LR) form, will be transcribed from worksheets or lab reports, but the visit date on the form should correspond to the date the form was initiated
- Staple relevant lab reports and worksheets to the data form; if your lab reports are transferred to you electronically, print a paper copy of the report and staple the copy to the case report form.

Calculations

- All calculations should be performed using a calculator
 - Values should be rounded according to the GpCRC data rounding rule (see section on data rounding rule, later in this chapter of the SOP)
-

7.5. Instruction box

- Each case report form includes an instruction box at the top of the first page. This instruction box gives the purpose of the form, when it should be completed, who administers the form, the respondent, and specific instructions for the form
-

7.6. Form skips, stops, caution ineligibility symbols

Skip pattern

- Form navigation (skip pattern) instructions are indicated in **boldface**. Skips are designated by an arrow from that response to a box with the number of the next item to be completed.

Stop sign

- Stops are indicated with an arrow from the response to a stop sign – instructions are given that must be fulfilled in order to continue with the form. For example, Form RG (Registration) asks if the patient has signed the consent form; if the response is “no”, the form is stopped with the instructions that *‘the consent form must be signed prior to continuing with screening’*.



Caution sign

- Items that require further review are indicated with an arrow from the response to a caution sign



Instructions are given regarding completion of the form when a caution is encountered

Ineligibility sign

- Ineligible conditions are designated by an arrow from the response to the symbol:



Other

- Other special instructions are indicated on the form in *italics*. Some examples are:
 - check only one*: only one of the listed responses should be checked
 - check all that apply*: one or more of the listed responses may be checked
 - specify*: a response should be printed on the line(s) provided
-

7.7. Headers and footers

- Each page of each form includes headers and footers which identify the form and the patient. The top right of the first page of each form has a space to check when the form is keyed [()keyed]. The top right of subsequent pages is reserved for the patient ID number. The footers include the form abbreviation, form revision number and date, the form name, and the page number. For example:

NORIG

Patient ID: __ __ __ __

Form RG

Revision 0 (29 Sep 06)

RG - Registration

Page 2 of 3

- The keyed box should be ☒ed when the form is keyed; the person keying the form should also date and initial the form by the keyed box
 - The patient ID number should be written on each page of the form
-

- The form and revision number will be printed on the forms in item 6; if a form is only used for one specific visit, the visit code will also be printed on the forms
- When a form revision affects the data that are collected, the form revision number and date will change; if this occurs, older revisions of that form should no longer be used for data collection
- If the form is revised without affecting the data collection - i.e., the wording of an item is revised - only the revision date of the form will be changed.

7.9. Missing data

- If a data item is missing and cannot be obtained when the form is completed or reviewed, write the appropriate code in the first left hand space of the empty data field:
 - ? = data temporarily missing or inconsistent; to be collected or resolved in the near future; items keyed with a ? will need to be followed up on and resolved
 - d = patient does not know the answer
 - n = not applicable in this situation
 - m = data missing
 - r = patient refused
 - When using any of the above codes, the entire data field does not need to be filled with the code (e.g., a missing height would be completed as m _ _ . _).
 - If data are missing on the form, an explanation for the missing values should be written on the form and keyed to the database in the General Comments section of the keying.
 - It is very important to keep the number of missing data items at a minimum, especially at baseline, since many future papers will depend on having a good set of baseline values. If an item is missing at the time the form is filled out, but is expected to be collected in the near future, use a '?' rather than the 'm' code for the item on the form. The 'm' missing code is for items that are truly missing. Coordinators are discouraged from using the 'm' code as a way to get through the data entry checks and enroll a patient; the screening windows should be broad enough to allow you to collect all data within the allotted time window. Also, if the data system will not accept a value because it is out of range, please contact the DCC, so we can make a determination as to whether the range checks need to be adjusted. In the meantime, use a '?' rather than an 'm' on the form. If there is a valid reason that a required baseline laboratory value is missing, please fax the Laboratory Results (LR) form to the DCC along with the reason for the missing value.
-

7.10. Administrative sign off

- Each form contains a section for administrative sign off
- These items include the Clinical Coordinator PIN and signature and the date the form was reviewed.
- Depending on the form, they may also include the PIN and signature of other staff

It is the standard of practice with NIH funded studies to certify study physicians who assume responsibility for the accuracy and integrity of the sponsored studies. Coordinators are certified separately based on their professional qualifications and privileges even though the functions fulfilled may overlap functions of the study physician.

On the NORIG data collection forms that require the Physician's signature, the signature is the assurance as the clinical center's principal investigator, that they are assuming responsibility for the accuracy of the data recorded on the study form. This does not require that the study physician completes the GpR forms or performs the procedures, but does require assumption of responsibility signified by signing the NORIG forms. This is also the standard of practice required by the FDA for case-report forms completion.

7.11. Handling forms

Form duplication

- The individual forms and form sets specific to a particular visit are available on the GpCRC website and on the data system (using the Print task)
- You should print forms from the website or data system as needed – if you print copies ahead of time, do not print huge quantities as forms may be revised, especially in the early days of a study

Form storage

- Forms for patients registered but not randomized in the NORIG trial should be kept in a single folder or binder in a locked room in a locked cabinet.
 - Each patient who is randomized in the NORIG trial will have a patient file – either a notebook or file folder which is kept in a locked room or locked filing cabinet. The patient file should contain all NORIG trial documents for the patient – consents, forms, appointment schedule, labels, randomization materials. The forms should be arranged in the notebook or folder chronologically by visit. Tabs can be used to separate the visits.
-

7.12. Data rounding rules

To round data, examine the digits following the last position required on the form:

- If the first digit following the last data position required for the response is less than 5, leave the digit in the last data position required for the response unchanged, e.g., if you need to round to , then 4.73 rounds to 4.7 and 1.44 rounds to 1.4
- If the first digit following the last data position required for the response is 5 or more, round up the digit in the last data position required for the response, e.g., if you need to round to , then 4.78 rounds to 4.8 and 4.75 rounds to 4.8

When completing a calculation for the NORIG trial, apply the rounding rule only at the last step, when required to record a quantity on the NORIG trial form.

7.13. Data audits and edits

Data audits

- The Data Coordinating Center will serve as the site monitor
- The Data Coordinating Center will conduct monthly data audits as a quality control measure
- Audits may be done by mail or on-site
- During an audit, the NORIG forms will be reviewed to see if they were completed and keyed correctly; the NORIG forms will also be checked against the source documents (laboratory results, electrocardiograms, gastric emptying breath test reports, electrogastrogram reports) to be sure that values were transcribed correctly.

Source documents include but are not limited to:

- Gastric emptying scintigraphy reports
- Upper endoscopy reports
- Gastric emptying breath test reports
- Electrogastrogram and satiety test reports
- Gastric imaging study reports
- Laboratory test result reports
- Electrocardiograms
- There are no source documents for questionnaires (the questionnaires are the original documents for the data collection)

Data edits

- Computerized data edits will be sent to the clinics monthly
- The data edits check for consistency and questionable values in the database.

Changes resulting from audits or edits

- Changes made to the NORIG forms as a result of an audit or an edit should be marked "per audit" or "per edit" and should be dated and initialed and keyed to the data system using the **Change a data form** > option under **Data Entry** >.
-

NORIG SOP Part I: Clinical Center Operations

8. Quality assurance

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8.1. Site visits

Purpose

- Conduct an audit of selected patient data
- Review documentation and procedures for the NORIG trial
- Tour facilities
- Discuss with clinical center personnel any problems that have occurred or that are expected to occur in conducting the trial

The following regulatory and study documents should be available or accessible:

- IRB communications including original approval letters, revision approvals, continuing review approvals, serious adverse event forms, and any communications regarding concerns or special requests from clinical center review board
- Signed and dated consent forms for all participants including the date and signature of a witness
- Documents including NORIG trial Protocol, PPMs, and SOPs
- Study forms for participants should be available for data audit

Participants

- At least two DCC personnel will attend the site visit. Representatives from NIDDK may also attend
- GpCRC certified staff from the clinical center

Reviewed during site visit

- IRB documentation
 - Original approval
 - Annual renewals (if applicable)
 - IRB submissions
 - Approval for updated consent forms and protocol
 - Unanticipated or serious adverse event reporting to local IRB
- NORIG trial documents
 - Consent forms
 - Directory
 - Drug accountability records
 - Protocol
 - PPMs
 - SOPs

8.1. Site visits

-
- Enrollment and retention
 - Status
 - Recruitment and retention strategies
 - Problems
 - Losses to follow-up
 - Personnel
 - Certification status
 - Personnel changes
 - Backup plans for personnel in event of absence
 - Clinical management
 - Adverse event reporting procedures
 - Study procedures
 - Clinical center coordination
 - Scheduling
 - Clinical center concerns or problems
 - Participant files
 - Security
 - Organization
 - Consent statements
 - Each patient's NORIG forms and their supporting source documents:
 - laboratory test results
 - gastric emptying report and scintigraphy on CD if available
 - upper endoscopy report
 - gastric emptying breath test report
 - electrogastrogram and satiety reports
 - Specimen shipment
 - Comparison of specimens expected and received
 - Shipping procedures and problems
 - Shipping supplies
 - Protocol performance
 - Protocol deviations
 - Exceptions for enrollment and visit window extensions
 - Exceptions on laboratory results obtained outside visit windows
 - Forms and data management
 - Monthly form status reports
 - Source documentation
 - Data audit (selected patients)
 - Eligibility criteria

8.1. Site visits

- Adverse events
 - Death reports
- Previous site visit report
 - Action items follow-up
 - Data audit follow-up

Site visit follow-up

- A list of action items is compiled at the end of the site visit to identify items which require further action. The procedure for site visit action item follow-up is:
 - Clinical centers will be required to respond to action items within 30 days of receipt of the site visit report. Responses should be in writing and sent to the CC.
 - The DCC will be required to respond to the action items within 30 days of the completion of the site visit report. The DCC will send a written report to the clinical center.
-

8.2. Performance monitoring

- The DCC will generate recruitment reports that will provide a count of participants screened and randomized at each clinical center
 - On a monthly basis, the DCC will generate reports summarizing the performance of all clinical centers. These reports will include information on enrollment and the percentage of expected visits for which documentation has been entered into the NORIG data system. Also, for those visits for which data have been entered, the report will show the percentage of missed visits, the completeness of data collection, the timeliness of data entry.
 - Performance reports will be reviewed by the Steering Committee, and the Steering Committee will make decisions regarding actions to be taken in the event that a clinical center is performing poorly.
-

8.3. Data quality surveillance

General procedures

- Quality assurance of data accuracy will occur routinely through three main procedures: data entry checks, monthly checks for completeness and edits, and form audits
- In addition, detection of problems may occur during data analysis. For example, in preparing reports for Steering Committee meetings, problems may be discovered. Outliers and unusual variations or patterns in the data are examined and may reveal problems.
- Quality assurance of data analysis is achieved by independent replication of key analyses within the DCC and review of reports by multiple individuals before distribution

Data entry checks

- The data system will contain checks during the data entry process of range, logic, and consistency of items within forms
- The data system will perform checks between forms to ensure that the same fields entered on different forms match
- A double data entry system will be used for all forms

Monthly check for completeness and edits

- On a monthly basis, DCC will generate a database report of:
 - number of participants randomized
 - missed visits
 - incomplete visits (missing or pending forms)
 - missed specimen collection or shipment
 - edits (see below)
- Edits are run on the database of the keyed forms monthly. Checks for missing, out-of-range, unusual and inconsistent values, cross-form checks and arithmetic errors are some of the types of checks performed. A listing of edits is sent to each clinical center for resolution within a month. The clinical center must respond to each edit on the listing, document appropriate changes to the forms and make corresponding changes in the database, and file the documentation with the edited data collection form. Items that cannot be corrected (e.g., missing values, unusual measures) are entered into a database at the DCC. These items are excluded from future edits. A hard copy of the edits, with each resolution should be kept in a notebook located at the clinical center.

8.3. Data quality surveillance**Forms audits**

On a monthly basis the DCC selects and requests copies of forms for specific participants be sent by each clinical center to the DCC for auditing

- Audited forms are compared with the database; discrepancies are noted and queried
 - Audited paper forms are also inspected for other problems, which are noted and queried
 - Each clinical center will be required to resolve discrepancies from the audit report and fax the resolutions to the DCC within 15 days
 - The DCC will generate a summary report of the audit discrepancies by clinical center to be distributed to all NORIG clinical centers
 - Discrepancy rates over time by clinical center are included in the monthly performance reports and are reviewed by the Steering Committee and the Data and Safety Monitoring Board
-

GpCRC

*Gastroparesis
Clinical Research Consortium*

**Nortriptyline for Idiopathic Gastroparesis
(NORIG)**

Standard Operating Procedures

**Part IV: Standards of Care for Patients
with Idiopathic Gastroparesis**

18 April 2008

NORIG SOP Part IV: Standards of Care**Contents**

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NORIG SOP Part IV: Standards of Care

1.Introduction

The purpose of this document is to describe a uniform set of practices to be applied by investigators in the Gastroparesis Clinical Research Consortium (GpCRC) in the evaluation and care of patients with idiopathic gastroparesis that are screened and enrolled in the Nortriptyline for Idiopathic Gastroparesis (NORIG) trial. These standards were developed so that patients with idiopathic gastroparesis will be evaluated uniformly before being placed in the NORIG trial. Once patients are in the NORIG trial, they will be treated in a generally standard fashion across clinical centers, thereby reducing the extent to which evaluation and care at a particular center will influence diagnosis, treatment, and outcome. In addition, these standards of care are written to delineate the tests and procedures used for routine clinical care of patients with idiopathic gastroparesis. These standards of care were derived by expert opinion as expressed by prior documents by the American Gastroenterological Association and the American Motility Society and refined by the consensus of investigators of the GpCRC. Every effort will be made to adhere to these standards of care for each patient.

NORIG SOP Part IV: Standards of Care

2. New patient with idiopathic gastroparesis

Each patient will be evaluated for idiopathic gastroparesis based on the following:

1. Presence of symptoms/signs of gastroparesis for at least 6 months of the past year.
2. Gastric emptying scintigraphy using a 4 hour low fat Egg Beaters meal as described by Tougas et al 2000¹. Delayed gastric emptying using 4 hour scintigraphy is considered with gastric retention at 2 hours postprandially to be >60% or at 4 hours to be >10%. General practice is to try to stop medications known to delay or accelerate gastric emptying for 3 days prior to the gastric emptying test.
3. Exclusion of gastrointestinal obstruction– generally performed with a careful history and physical examination, laboratory testing, radiographic evaluation, and upper endoscopy.
4. Exclusion of diabetes history

Although there are general guidelines for the evaluation of patients with gastroparesis^{2,3}, the exact evaluation of a patient may differ depending on the individual case characteristics.

Initial evaluation of a patient with suspected idiopathic gastroparesis

History

Gastric symptoms: dominant and associated symptoms (nausea, vomiting, pain/discomfort, early satiety, fullness, bloating), duration, frequency, onset (abrupt vs. insidious), course, precipitating/relieving factors. Nature of symptoms: cyclic vs. non-cyclic. If cyclic; are cycles regular or not.

Extragastric symptoms: Other GI symptoms (diarrhea, constipation), anorexia, weight loss, dehydration, orthostatic symptoms

History of infectious disorders with resultant chronic upper GI motility symptoms.

Assessment of nutritional status

Dietary intolerance

Other disorders – especially those that might relate to symptoms of gastroparesis (e.g. collagen vascular disease, endocrine diseases such as hypothyroidism)

Symptoms or diagnosis of overlap syndromes: migraine headaches, fibromyalgia, interstitial cystitis, endometriosis, depression.

Hospitalizations/emergency room visits for intractable symptoms (frequency/yr)

Other medical problems- seizures, cardiac arrhythmias, glaucoma

Family history of gastroparesis, GI motility disorders, overlap syndromes

Review of current medications

Clinical response to present and past medications given for patient's symptoms: acid suppressants, antiemetics, prokinetics, tricyclic antidepressants, analgesics

Document use of selective serotonin reuptake inhibitors (SSRIs), calcium channel blockers, monoamine oxidase inhibitors (MAOIs)

Physical examination

Vital Signs: blood pressure, pulse, temperature, weight, height, body mass index (BMI)
Optional: Orthostatic vital signs
Abdominal examination: visible distention, tympany, succussion splash, tenderness, organomegaly
Rectal examination with assessment of occult fecal blood
Documentation of recent gynecologic exam by internist or gynecologist
Electrocardiogram

Laboratory tests

Complete blood count including white blood cell count, red blood cell count, white blood cell differential, hemoglobin, hematocrit, platelet count, erythrocyte sedimentation rate
Complete metabolic panel, including sodium, potassium, chloride, carbon dioxide, glucose, calcium, phosphate, BUN, creatinine, uric acid, albumin, total protein
Thyroid function tests, thyroid stimulating hormone (TSH)
Pregnancy test
Optional tests (obtained in part on the particular patient):
Blood tests:
- HbA1c, liver chemistries, (e.g. SPEP, amylase and/or lipase), anti-nuclear antibody, C-reactive protein, pregnancy test, magnesium, tissue transglutaminase antibody, fasting cortisol, paraneoplastic antibody panel
Urinalysis (if clinically indicated)

Radiology

Abdominal obstruction series, if suggested by history (profound pain, bloating, or vomiting) or physical examination (distention, tympany)
Abdominal right-upper quadrant ultrasound to rule out gallbladder, liver, and pancreatic disease, if suggested by history, physical examination (RUQ pain or tenderness), or laboratory findings (elevated liver chemistries)

Endoscopy

Upper endoscopy (must have been done within 2 years prior to registration in NORIG).
Esophageal, gastric and duodenal biopsies may be obtained (if indicated by history, physical examination (associated bloating, diarrhea, or family history of celiac disease), or laboratory findings (unexplained microcytic anemia)

Nuclear medicine

Gastric emptying scintigraphy (Solid phase - % retention at 0, 0.5, 1, 2, 3, 4 hrs). Must have been done at a GpCRC clinical center within 2 years prior to registration. Required standardized test meal and test procedures are outlined in NORIG SOP Part I: Clinical Center Operations.

Other tests which may be obtained

Electrogastrogram by fast Fourier and/or signal averaging analysis

With meal – water load, Ensure, or egg sandwich

¹³C-Spirulina breath test

Antroduodenal manometry (to exclude associated small intestinal dysmotility)

Small bowel radiographic examination (to exclude mechanical lesions of the small intestine):

Small Bowel Follow-Through, Enteroclysis, Computer Tomographic Enterography

Small intestinal transit testing: Scintigraphy, small intestinal barium series, lactulose breath testing

Hydrogen breath testing (to exclude small intestinal bacterial overgrowth)

Sitzmarker study, in patients with lower bowel complaints

Anal manometry and/or anal EMG, balloon evacuation

Urodynamic evaluation, in patients with urinary symptoms

Psychometric and quality of life measures, including

Gastroparesis Cardinal Symptom Index (GCSI), Brief Pain Inventory (PI), (Beck Depression Inventory (BDI-II), health survey (SF-36) and Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)

Autonomic testing – standard cholinergic and adrenergic or 24 hour Holter for heart rate variability, giving an assessment of high and low frequency power

Treatment

- The general principles for treatment of idiopathic gastroparesis are to (1) correct fluid, electrolyte, and nutritional deficiencies; (2) identify and rectify the underlying cause of gastroparesis if possible; and (3) reduce symptoms⁴.
- The patient's medication list should be reviewed to eliminate drugs that might exacerbate the underlying dysmotility disorder or prevent the beneficial actions of a prokinetic agent.
- Primary treatment of idiopathic gastroparesis includes dietary manipulation and the administration of antiemetic and/or prokinetic therapies.
- A baseline gastroparetic instruction sheet will be given to the patients with suggestions to follow. Additional treatments for refractory symptoms or if pain is a dominant symptom may include the use of tricyclic antidepressants and/or analgesic medications. Occasionally newer agents (Cymbalta or Lyrica) are tried on an off label basis.
- For relatively mild disease, dietary modifications and intermittent administration of a low-dose antiemetic or prokinetic agent may provide satisfactory control of symptoms.

- Patients with more severe manifestations of gastroparesis, such as refractory vomiting, or pronounced dehydration might require hospitalization, intravenous hydration, nasogastric suction to decompress the stomach and/or intravenous administration of antiemetic and prokinetic agents.
 - Consideration of surgically or endoscopically placed enteral tubes for feeding and/or venting
 - Surgical options (gastric electrical stimulation, jejunostomy placement) are considered for persistently refractory cases.
 - Other medications can be given for related overlap symptoms, such as for migraine headaches.
-

NORIG SOP Part IV: Standards of Care

3. Follow-up visits

The frequency of follow-up visits depends on the need for diagnostic testing, the severity of symptoms and complications of gastroparesis, responses to therapy, and complications of prescribed treatments.

Patients will be seen every three weeks for a total of 18 weeks by the gastroenterologist to evaluate for changes in clinical course, symptoms and possible side effects. These follow-up visits will include an interim medical history, review of symptoms, updated medication list, physical examination, diagnostic tests, and discussion of adherence to the study drug regimen as well as standard of care recommendations.

Items for documentation

History

- Review of disease course
- Assessment of current symptoms
- Assessment of nutritional status
- Other disorders and surgeries
- Review of current medications
- Response to any treatment given since last visit
- Psychosocial history – document any changes

Physical examination

- Vital Signs: blood pressure, pulse, temperature, weight, height, body mass index (BMI)
- Optional: orthostatic vital signs
- Abdominal examination: tenderness, succussion splash
- Electrocardiogram

Laboratory tests

- Complete blood count, complete metabolic panel, thyroid function tests
- Optional: Erythrocyte sedimentation rate, magnesium, amylase/lipase C-reactive protein, urinalysis
- Optional: Abdominal obstruction series

Treatment considerations

Discuss trial treatment groups, test procedures to be done such as the electrogastrogram, satiety test and gastric emptying breath test, the use of daily medications as well as rescue medications for nausea, vomiting and pain that are allowed during the trial. Consider additional treatment with hydration, nutrition, antiemetic agents, prokinetic agents, analgesic agents, botulinum toxin, and gastric electric stimulation if needed. Consider home intravenous (IV) medications if symptoms are particularly severe and/or cyclic.

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4. Dietary and nutritional recommendations

Gastroparesis, or paralysis of the stomach, refers to a stomach that empties slowly. Gastroparesis is characterized by symptoms from the delayed emptying of food, namely: bloating, nausea, vomiting or feeling full after eating only a small amount of food. Gastroparesis can occur as a result of several conditions. However, in many individuals with gastroparesis, the cause of the disorder is not known. This subset of patients are classified as idiopathic gastroparetics. Many present with an abrupt onset of symptoms, sometimes in association with acute gastroenteritis or other non-specific illness, and it is presumed that this may represent a post-viral syndrome. Gastroparesis is more common in women and can have a major impact on quality of life.

The general principles for treating symptomatic gastroparesis involve several strategies. First, attempts are made to correct fluid and nutritional deficiencies that may have occurred from chronic nausea and vomiting, and/or the inability to eat normally. Second, treatments are given for the unpleasant symptoms that accompany gastroparesis. Third, the underlying cause of idiopathic gastroparesis, such as thyroid disorders, etc., is treated if possible. The treatment of patients with idiopathic gastroparesis generally relies on dietary modifications, medications that enhance gastric emptying, and medications that reduce nausea and vomiting.

A number of dietary recommendations have been developed based on the understanding of normal stomach emptying of different types of foods. These dietary recommendations are likely to be of greatest benefit to those with mild to moderate disease, but are also tried in patients with more severe gastroparesis to complement other medical treatments. It is recommended that anyone with gastroparesis, but especially those with other medical problems such as kidney disease, seek dietary counseling with a dietician to help individualize nutrition therapy and maximize nutritional benefits.

Basic dietary guidelines:

- Small, frequent meals. Reducing the meal size reduces the distention of the stomach from the meal. By eating smaller meals, patients may not feel as full or bloated and the stomach may empty faster. With the reduction in meal size, increasing the number of meals to 4-6 per day is needed to maintain adequate nutritional intake.
- Avoid foods high in fat. Fat can delay emptying of the stomach. Eating less fat-containing foods will decrease the amount of time food stays in the stomach. However, fat-containing liquids, such as milkshakes, may be tolerated and provide needed calories.
- A diet low in fiber is suggested. Fiber delays gastric emptying. In addition, fiber may bind together and cause a blockage of the stomach, called a bezoar in some patients. Examples of high fiber foods that should be avoided include oranges, berries, green beans, potato peels, apples, sauerkraut, and Brussel sprouts. Fiber supplements for treatment of constipation should also be discontinued if possible.

- Chew food well before swallowing. Patients should avoid foods that may not easily be chewed such as broccoli, corn, popcorn, nuts, and seeds. Solid food in the stomach does not empty well. Dental problems, such as missing or broken teeth, may lead to poorly chewed food; this may add to the problem of inadequate breakdown of food into smaller particles in the stomach for passage into the small intestine for absorption.
- Taking fluids throughout the meal and sitting upright or walking for 1-2 hours after meals may help in the emptying of the meal from the stomach.
- A daily multivitamin/mineral supplement can be taken if dietary intake is inadequate.

If these measures are ineffective, the patient may be advised to consume the bulk of their meals as semi-solids or liquids, such as puréed foods or soups. Stomach emptying of liquids is often normal in patients with gastroparesis. Calorie-containing drinks, such as Hawaiian Punch or Hi-C, provide fluid and calories, hence are better than water alone. Some options while on a liquid diet include milk, instant breakfast, milkshakes, yogurt, puddings, custard, cereals, and smoothies. To meet the nutritional needs of patients, it may be necessary to supplement the diet with a commercially available liquid nutrient preparation that is low in fiber such as Ensure, Boost, or even baby foods. Blenderized foods prepared by the patient may also be used as a liquid nutrient source. Any food can be blenderized; solid foods will need to be thinned with some type of liquid, such as broth, milk, juice, water. The blender should be cleaned well after each use.

There are quite a few medications that can delay stomach emptying. Check if any of the medications the patient is taking could be slowing down the stomach emptying.

Patients with kidney disease need to follow additional dietary advice. The dietary restrictions will depend on nephrologist's assessment. Adequate protein is needed for nourishment, but too much may increase a waste product called urea that kidneys may not be able to get rid of. High sodium (salt) intake can increase blood pressure and fluid retention. Restriction of potassium varies depending on the stage of kidney disease. Generally, one should avoid high potassium foods such as bananas, oranges, kiwi, leafy greens, and broccoli. Kidneys may not be able to remove phosphorus from the blood. High phosphorus foods include dried beans, peas, nuts, and liver.

Patients with chronic symptoms of gastroparesis, despite these attempts at dietary intervention and medication, may develop dehydration and malnutrition. Occasionally, patients need an alternative method to obtain fluid and nutrition. This might involve delivering fluids and nutrients directly into the small intestine, bypassing the stomach, using a jejunostomy tube. In severe cases, intravenous fluids and nutrition may need to be provided.

Table 1: Dietary Recommendations for Gastroparesis

Eat smaller, more frequent meals
Eat less fatty foods
Avoid fiber
Avoid foods that cannot be chewed well.

Table 2: Additional dietary recommendations for gastroparesis

Liquid nutrients are better tolerated over solid food
Avoid medications that can delay stomach emptying such as:
 Aluminum-containing antacids (Amphojel)
 Narcotic pain medications (Percocet, Tylenol #3, Tylox, Oxycontin, and others)
 Anticholinergic agent (Bentyl, Levsin, Elavil, and others)
 Bulk-forming agents (Metamucil, Perdiem, Fibercon, and others)

Table 3: Foods that are encouraged

Breads, cereals, crackers, ground or pureed meats
Vegetables – cooked and, if necessary, blenderized/strained
Fruits – cooked and, if necessary, blenderized/strained
Juices, beverages, milk products, if tolerated

Table 4: High fiber foods that should be avoided in gastroparesis

Fruits - apples, berries, coconuts, figs, oranges, persimmons,
Vegetables - Brussel sprouts, green beans, green peas, lettuce, potato peels, sauerkraut
Bran/whole grain cereals
Nuts and seeds
Legumes/dried Beans – baked beans, lentils, soy beans

A sample diet for patients with gastroparesis: sample meal plan for 6 small meals

Breakfast	1 cup cream of wheat cereal ½ cup skim milk ½ cup grape juice 1 scrambled egg
Snack	10 ounces of instant breakfast with skim milk
Lunch	½ cup vegetable soup ½ turkey sandwich ½ cup applesauce ½ cup milk 1 tablespoon mayonnaise
Snack	10 ounces banana shake made with 1 plain or vanilla yogurt, milk and sugar
Dinner	2-3 ounces baked chicken or fish ½ cup mashed potatoes 1 teaspoon margarine ½ cup spinach ½ cup milk ½ cup fruit cocktail
Snack	½ cup pudding, custard or gelatin

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